COMBINATIVE RANK-BASED TESTS FOR COMPARING RESPONSE RATES AND RESPONSE DURATIONS IN RANDOMIZED CLINICAL TRIALS

By

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To my parents,

my sisters,

the Late Mrs. Annette Kendall Katzoff

and all those afflicted

by Alzhiemer's Disease or other kinds of dementia

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In randomized clinical trials, one could be interested in testing a location shift in the distribution of "response durations" after a drug has been administered, and a location shift in the log-odds of "response rates" between two groups (men-women or treatment-control). Often such tests are carried out separately. Another approach in analy]zing data in the above structure is by pooling the nonresponders with responders and performing a classical two-sample test for right censored data by assigning nonresponders with response durations equal to 0. Owing to a lack of power in both the above approaches we propose a rank-based Locally Most Powerful Test (LMPT) for testing the two hypotheses simultaneously.

The test statistic is represented as a stochastic integral, and martingale theory is used for deriving asymptotic properties of the test statistic under of contiguous sequence alternatives. A Monte Carlo study shows that the proposed tests are more powerful than traditional tests under a variety of conditions. Settings resulting in a LMPT, viability, and scope of application are also discussed.

CHAPTER 1
INTRODUCTION

1.1 The Problem

In drug efficacy trials a drug may be evaluated on the basis of its respponse rate and response duration. In particular, researchers may be interested in comparing the proportion of responders and the response duration of responding subjects from two populations. For instance, in cancer clinical trials one may be interested in comparing two treatments on the basis of the proportion of subjects who achieve remission as well as the duration of remission for those subjects who have achieved remission. In an industrial setting one could be interested in comparing two manufacturing processes on the basis of the rate of non-defective products as well as the life-length of non-defective items. In both examples, there are two end points: one associated with the proportion and the other associated with failure times, possibly right censored.

1.2 Common Practice

Two common approaches for comparing two samples based on response rates and response durations are

1. Separate two-sample tests comparing proportions and the response durations are performed. In this dissertation these tests will be called "separate" tests.

2. The subjects who fail to respond are treated as uncensored responders with response duration zero, and a two-sample test for right censored data is performed. From here on, these tests will be referred to as "pooled" tests.

A goal of this dissertation is to demonstrate that separate tests are likely to be less powerful than "pooled" tests. However, it will also be shown that pooled tests are not always the most powerful. A new two-sample combined test based on response rates and response durations is proposed. Combined tests will be shown to be locally most powerful under specific settings.

1.3 Literature Review

Linear rank statistics (Prentice 1978) have been developed for tests on regression coefficients with censored survival data. These statistics arise as score statistics based on the marginal probability of a generalized rank vector.

Let us consider the following two-sample life testing situation. We have on test L subjects, L_1 of them from population 1 and $L_2 = L - L_1$ from population 2. Assume no ties among uncensored observations. Let $t_{(1)} < \cdots < t_{(k)}$ be the distinct ordered survival times for the uncensored subjects in the combined sample and let m_i be the number of subjects censored in the interval $[t_{(i)}, t_{(i+1)})$, for $i = 0, \cdots, k$, where $t_{(0)} = -\infty$ and $t_{(k+1)} = \infty$. Let $z_{(i)} = 0$ or 1 according to whether the subject failed at $t_{(i)}$ is from population 1 or 2 and similarly let $z_{(ij)}$, for $j = 1, \cdots, m_i$, be the corresponding sample indicators for the m_i subjects censored in the interval $[t_{(i)}, t_{(i+1)})$. Note that $L = k + \sum_{i=0}^{k} m_i$. Finally, let n_{1i} be the number of population I subjects and n_i be the total number of subjects, at risk at time $t_{(i)}-$.

Let us fix the somewhat nonstandard notation in relation to the definition of a generalized rank vector, $\boldsymbol{R}$, associated with censored and uncensored observations, with the aid of the following example. Suppose the values of our observations are $112, 69^+, 32, 112^+$ with $^+$ indicating censoring. Then we have $t_{(1)} = 32$, $t_{(2)} = 112$, $t_{11} = 69$, $t_{21} = 112$. Kalbfleisch & Prentice (1973) take the point of view that it is the rank vector of the underlying uncensored values $t_{(i)}$, that are only partially observed because of censoring, is of primary interest. For instance, the rank vector underlying

the above example is known to be an element of the following set of arrangements of ranks of the observations:

$$\{(3,2,1,4),(3,1,2,4),(3,1,4,2)\}, \tag{1.1}$$

where $(3,2,1,4)$ indicates that the 3rd., the 2nd., the 1st., and the 4th. individuals have the ranks 1, 2, 3, and 4, respectively. The generalized rank vector $\boldsymbol{R} = (R_1, \cdots, R_k)$ is the collection of possible underlying rank vectors such as in (1.1). The probability of $\boldsymbol{R}$ is the sum of the probabilities of the underlying rank vectors.

For the two-sample setting Prentice (1978) considered the accelerated failure time model

$$y = \theta + \beta z + \sigma \nu, \tag{1.2}$$

where $y = \log(t)$, for the event time t; θ, β and σ are parameters; z is the population indicator; ν is a random variable with density function $f(w)$ and survival function $F^*(w) = \int_w^\infty f(u)du$. Prentice derived the rank-based LMPT for testing the hypothesis $H_0 : \beta = 0$, which implies that the distribution functions for the two populations are the same. Let Γ_k be the region $0 < u_1 < \cdots < u_k < 1$,

$$\phi(u) = \frac{f'\{(F^*)^{-1}(1-u)\}}{f\{(F^*)^{-1}(1-u)\}},$$

and

$$\Phi(u) = -\frac{f\{(F^*)^{-1}(1-u)\}}{1-u}.$$

Prentice's statistic has the form:

$$T_P = \sum_{i=1}^{k} \left(c_i z_{(i)} + C_i s_i \right), \tag{1.3}$$

where $s_i = \sum_{j=1}^{m_i} z_{ij}$,

$$c_i = \int_{\Gamma_k} \phi(u_i) \prod_{j=1}^{k} \{n_j(1-u_j)^{m_j} du_j\} = E\{\phi(u_i)\} \tag{1.4}$$

and

$$C_i = \int_{\Gamma_k} \Phi(u_i) \prod_{j=1}^{k} \{n_j(1-u_j)^{m_j} du_j\} = E\{\Phi(u_i)\} \tag{1.5}$$

. prentice (1978) derived expressions for c_i and C_i for specific densities f using the relationship

$$E\{(1-u_i)^{\rho}\} = \prod_{j=1}^{i} \left(\frac{n_j}{n_j+l}\right). \tag{1.6}$$

Note that with scores c_i and C_i generated by the true underlying density function, the test based on T_P is locally most powerful. If the underlying density is misspecified, T_P can still be used for testing H_0 but the loss of efficiency, however, may be a concern. The problem of asymptotic relative efficiency has been discussed by several authors including Birnbaum & Laska (1967), Gastwirth (1970) (pages 89-109), Lee et al. (1975), Prentice (1978), and Leurgans (1983).

1.3.1 Some Special Cases of T_P

1. For the logistic density $f(x) = e^x(1+e^x)^{-2}, \quad -\infty < x < \infty$,

   $$\phi(u) = 2u - 1 \text{ and } \quad \Phi(u) = u.$$

   Using (1.6),

   $$E\{(1-u_i)\} = \prod_{j=1}^{i} \left(\frac{n_j}{n_j+1}\right) = \tilde{S}(t_{(i)}).$$

   Hence

   $$c_i = 1 - 2\tilde{S}(t_{(i)}) \tag{1.7}$$

and

$$C_i = 1 - \tilde{S}(t_{(i)}). \tag{1.8}$$

Note that $\tilde{S}(t)$ is the estimator of $F(t)$, slightly different from the Kaplan-Meier (1958) estimator. The statistic T_P takes the form:

$$T_{PP} = \sum_{i=1}^{k} \Big[z_{(i)} \big\{ 1 - 2\tilde{S}(t_{(i)}) \big\} + s_i \big\{ 1 - \tilde{S}(t_{(i)}) \big\} \Big], \tag{1.9}$$

which is the Peto & Peto (1972) generalization of Wilcoxon statistic. In the case when there are no censored observations

$$T_{PP} = -\sum_{i=1}^{L} \Big(z_{(i)} (2i(L+1)^{-1} - 1) \Big) = -\frac{2}{L+1} \Big\{ \sum R_i - \frac{L_1(L+1)}{2} \Big\}, \tag{1.10}$$

where R_i's are the ranks of the observations from sample 1.

2. Under the extreme minimum value density

$$f(x) = e^{(x - e^x)}, \qquad -\infty < x < \infty,$$

$$\phi(u) = -\log(1-u) - 1 \text{ and } \quad \Phi(u) = -\log(1-u).$$

Again

$$E\{\log(1-u_i)\} = -\sum_{j=1}^{i} n_j^{-1}.$$

Hence

$$c_i = \sum_{j=1}^{i} n_j^{-1} - 1 \tag{1.11}$$

and

$$C_i = \sum_{j=1}^{i} n_j^{-1}. \tag{1.12}$$

The statistic T_P takes the form:

$$T_L = \sum_{i=1}^{k} \left[z_{(i)} \left\{ \sum_{j=1}^{i} n_j^{-1} - 1 \right\} + s_i \sum_{j=1}^{i} n_j^{-1} \right]. \tag{1.13}$$

When there is no censoring then the statistic takes the form:

$$T_L = \sum_{i=1}^{n} z_{(i)} \Big(\sum_{j=1}^{i} n_j^{-1} - 1 \Big).$$

which is the well-known logrank or the Savage (1956) statistic.

1.3.2 An Alternative Representation of T_P

Prentice & Marek (1979) expressed T_P in terms of observed and conditionally expected number of failures (conditional on the total size of the risk sets, at a given failure time). They set

$$w_i = n_i(C_{i-1} - C_i), \quad i = 1, \cdots, k \tag{1.14}$$

with $C_0 = 0$. Substitution in equation (1.3) yields,

$$T_P = \sum_{i=1}^{k} z_{(i)}(c_i - C_i - w_i) + \sum_{j=1}^{k} w_j(z_{(j)} - n_{1j}n_j^{-1}). \tag{1.15}$$

Note that the second term in equation (1.15) is a weighted sum of observed number of failures, $z_{(j)}$, in the treatment group at $t_{(j)}$ minus the conditionally expected number of failures, $n_{1j}n_j^{-1}$, given the risk set sizes n_{1j} and n_j and under H_0. If

$$n_i C_{i-1} = c_i + (n_i - 1)C_i, \quad i = 1, \cdots, k, \tag{1.16}$$

then the first term in (1.15) equals 0 and T_P has a particularly attractive form in terms of observed and expected number of failures. It can be shown that the scores

corresponding to T_{PP} and T_L (see equations (1.9) and (1.13)) satisfy condition (1.16). For scores generated from the logistic density as given in equations (1.7) and (1.8),

$$\begin{aligned}
n_i C_{i-1} &= n_i \Big\{1 - \prod_{j=1}^{i-1} \frac{n_j}{n_j+1}\Big\} \\
&= 1 - 2\prod_{j=1}^{i} \Big(\frac{n_j}{n_j+1}\Big) + (n_i - 1)\Big\{1 - \prod_{j=1}^{i} \Big(\frac{n_j}{n_j+1}\Big)\Big\} \\
&= n_i - (n_i + 1)\prod_{j=1}^{i} \Big(\frac{n_j}{n_j+1}\Big) \\
&= c_i + (n_i - 1)C_i. \qquad (1.17)
\end{aligned}$$

Hence,

$$T_{PP} = T_{PM-PP} = \sum_{i=1}^{k} w_i\Big(z_{(i)} - \frac{n_{1i}}{n_i}\Big), \qquad (1.18)$$

where $w_i = n_i(C_{i-1} - C_i) = c_i - C_i = -\tilde{S}(t_{(i)})$. Using similar arguments, it is easy to show that scores generated from the extreme minimum value density also satisfy condition (1.16). Hence,

$$T_L = T_{PM-L} = -\sum_{i=1}^{k} \Big(z_{(i)} - \frac{n_{1i}}{n_i}\Big) \qquad (1.19)$$

Mehrotra et al. (1982) in a study of relationship between T_P and T_{PM} show that, in general, the optimal scores, c_i and C_i, given by Prentice (1978) do satisfy (1.16).

CHAPTER 2
TOPIC OF RESEARCH

2.1 Data Structure

Assume that the number of subjects available in Group 1 and Group 2 are L_1 and L_2 ($L = L_1 + L_2$) and that the number of responders in Group 1 and Group 2 are K_1^* and K_2^* respectively, where both K_1^* and K_2^* are random ($K_1^* + K_2^* = K^*$). Clearly, when referring to responders, K^* is the size of the risk set at time 0 in the combined sample. Conditional on $K_1^* = k_1^*$ and $K_2^* = k_2^*$, we are able to observe "response durations" from each group. Let k_1 and k_2 be the number of uncensored response durations in the respective groups ($k = k_1 + k_2$). Note that $k_i \leq k_i^*$, $i = 1, 2$, and $k \leq k^*$. Assume no ties among uncensored response durations. Let $X_{(1)}, \cdots, X_{(k)}$ be the ordered uncensored log-response durations in the pooled sample. Let $(X_{i1}, \cdots, X_{im_i})$ be the unordered censored log-response durations in $[X_{(i)}, X_{(i+1)})$, $i = 0, \cdots, k$, where $X_{(0)} = -\infty$ and $X_{(k+1)} = \infty$. Note that $k^* = k + \sum_{i=0}^{k} m_i$. Also, let $z_{(i)}$s and z_{ij}s be the group indicators associated with $X_{(i)}$s and X_{ij}s, respectively. Let the response rates in the respective groups be p_1 and p_2. Assuming that distribution functions for response durations, F_1 and F_2, are absolutely continuous, let the corresponding densities in the respective groups be f_1 and f_2.

2.2 Hypotheses of Interest

We consider the following null hypothesis H_0 and the alternative hypothesis H_Δ.

$$H_0 : f_1(x) = f_2(x) = f(x) \text{ and } p_1 = p_2 = p, \tag{2.1}$$

versus

$$H_\Delta : \begin{cases} f_1(x) = f(x + c\alpha_1\Delta) \\ f_2(x) = f(x - c\alpha_2\Delta) \\ \text{or} \\ \log \frac{p_1(1-p)}{p(1-p_1)} = -\beta_1\Delta d \\ \log \frac{p_2(1-p)}{p(1-p_2)} = +\beta_2\Delta d, \end{cases} \tag{2.2}$$

where Δ, c, d, α_i and β_i $(i = 1, 2)$ are nonnegative parameters with $\alpha_1 + \alpha_2 = \beta_1 + \beta_2 = 1$. Under H_Δ,

$$f_2(x) = f_1(x - c\Delta)$$

and

$$\log \frac{p_1(1 - p_2)}{p_2(1 - p_1)} = -d\Delta.$$

Note that the key issue in the above alternative hypothesis is that c need not be equal to d. In other words, the degree of shift in the failure times distributions and that in the log-odds ratios could be different.

Effectively we will be interested in testing the hypotheses $H_0 : \Delta = 0$ vs $H_\Delta : \Delta > 0$. Owing to the nature of the hypotheses it is reasonable to derive a LMPT. The following section discusses the derivation of the LMPT statistic.

2.3 Derivation of the Locally Most Powerful Test

In the uncensored data case Chang et al. (1994) defined the burden-of-illness as the sum of severity scores over all cases in each group. In their context, burden-of-illness represented a measure of total morbidity due to the disease in each group. The test proposed by Chang et al. (1994), however, is sensitive to the severity scoring method. In particular, the test may have poor local power when the underlying distribution of severity score has heavy tails. One alternative is to use the ranks of the severity scores instead of their actual measurements. In this manuscript, severity scores correspond to response duration.

The generalized rank vector $\boldsymbol{R}$, as discussed in section 1.3, plays a crucial role in the construction of the LMPT. Rank-based tests are robust to misspecification of the underlying distribution of response durations.

In order to derive the locally most powerful test we will use the Neyman-Pearson (N-P) lemma. By the N-P lemma, the statistic for testing H_0 versus a fixed H_Δ is

$$\frac{P_{H_\Delta}(K_1^* = k_1^*, K_2^* = k_2^*, \boldsymbol{R} = \boldsymbol{r})}{P_{H_0}(K_1^* = k_1^*, K_2^* = k_2^*, \boldsymbol{R} = \boldsymbol{r})}$$

$$= \left\{\frac{P_{H_\Delta}\left(\boldsymbol{R} = \boldsymbol{r} | K_1^* = k_1^*, K_2^* = k_2^*\right)}{P_{H_0}\left(\boldsymbol{R} = \boldsymbol{r} | K_1^* = k_1^*, K_2^* = k_2^*\right)}\right\}\left\{\frac{P_{H_\Delta}\left(K_1^* = k_1^*, K_2^* = k_2^*\right)}{P_{H_0}\left(K_1^* = k_1^*, K_2^* = k_2^*\right)}\right\}. \tag{2.3}$$

The contents within the first curly brackets of equation (2.3), denoted as $p_\Delta(\boldsymbol{r})/p_0(\boldsymbol{r})$, will be addressed. By Taylor's expansion, in the notation of Prentice (1978),

$$p_\Delta(\boldsymbol{r}) = p_0(\boldsymbol{r}) + \Delta \frac{dp_\Delta(\boldsymbol{r})}{d\Delta}\bigg|_{\Delta=0} + \Delta o(1).$$

Dividing both sides by $p_0(\boldsymbol{r})$, we have

$$\frac{p_\Delta(\boldsymbol{r})}{p_0(\boldsymbol{r})} = 1 + \Delta\left\{\frac{1}{p_\Delta(\boldsymbol{r})}\frac{dp_\Delta(\boldsymbol{r})}{d\Delta}\right\}\bigg|_{\Delta=0} + \Delta o(1). \tag{2.4}$$

Indeed, $p_\Delta(\boldsymbol{r}) = P_{H_\Delta}\Big(\boldsymbol{R} = \boldsymbol{r} | K_1^* = k_1^*, K_2^* = k_2^*\Big)$ is the probability of the (random) rank vector, $p(\boldsymbol{r})$, in the notation of Prentice (1978) and can be expressed as

$$
\begin{aligned}
p_\Delta(\boldsymbol{r}) &= P_{H_\Delta}\Big(\boldsymbol{R} = \boldsymbol{r} | K_1^* = k_1^*, K_2^* = k_2^*\Big) \\
&= \int_{\Gamma_k} \prod_{i=1}^{k} \Bigg[\; f\Big(x_{(i)} - c\Delta(z_{(i)} - \alpha_1)\Big) \prod_{j=1}^{m_i} \Big\{ 1 - F\Big(x_{(i)} - c\Delta(z_{(ij)} - \alpha_1)\Big) \Big\} dx_{(i)} \; \Bigg],
\end{aligned}
\tag{2.5}
$$

where Γ_k is the region $x_{(1)} < \cdots < x_{(k)}$. In equation (2.5) we are making the assumption that all censoring happens at the left end point of each interval of censoring, i.e., $x_{ij} = x_{(i)}+, \forall j = 1, \cdots, m_i$. By straightforward calculations,

$$
p_0(\boldsymbol{r}) = P_0\Big(\boldsymbol{R} = \boldsymbol{r} | K_1^* = k_1^*, K_2^* = k_2^*\Big) = \frac{1}{\prod_{i=1}^{k} n_i}, \tag{2.6}
$$

where n_i is the size of the risk set at log-time $t_{(i)}-$. Following equations (2.4), (2.5), (2.6), and the approach on page 170 of Prentice (1978),

$$
\frac{p_\Delta(\boldsymbol{r})}{p_0(\boldsymbol{r})} = 1 + \Delta c \Big\{ \sum_{i=1}^{k} \Big(z_{(i)} c_i + \sum_{j=1}^{m_i} z_{ij} C_i \Big) \Big\} + \Delta o(1), \tag{2.7}
$$

where $o(1) \to 0$ as $\Delta \to 0$,

$$
c_i = \int_{\Gamma_k} \left(- \frac{d \log f(x_{(i)})}{dx_{(i)}} \right) \prod_{i=1}^{k} \Big\{ n_i f(x_{(i)}) F^{m_i}(x_{(i)}) dx_{(i)} \Big\}, \tag{2.8}
$$

and

$$
C_i = \int_{\Gamma_k} \left(- \frac{d \log F(x_{(i)})}{dx_{(i)}} \right) \prod_{i=1}^{k} \Big\{ n_i f(x_{(i)}) F^{m_i}(x_{(i)}) dx_{(i)} \Big\}. \tag{2.9}
$$

In the derivation of equation (2.7), we have used the fact that $\sum_{i=1}^{k} (c_i + m_i C_i) = 0$. Note that the second term in equation (2.7) does not depend on the choice of α_1 and

α_2. In equation (2.7), c_i is the score for an uncensored observation and C_i is the score for a censored observation at $x_{(i)}+$. The content in the second curly brackets of equation (2.3) is

$$\begin{aligned}
&\frac{P_\Delta\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big)}{P_0\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big)} \\
&= \; 1 + \Delta\left\{\frac{1}{P_0\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big)} \frac{dP_\Delta\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big)}{d\Delta}\bigg|_{\Delta=0}\right\} \\
&+ \; \Delta o(1). \qquad (2.10)
\end{aligned}$$

Clearly, $P_0\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big) = P_0\Big(K_1^* = k_1^*\Big)P_0\Big(K_2^* = k_2^*\Big)$ is the product of two binomial probabilities:

$$P_0\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big) = \binom{L_1}{k_1^*}\binom{L_2}{k_2^*}p^{k^*}(1-p)^{L-k^*}. \qquad (2.11)$$

Similarly,

$$P_\Delta\Big(K_1^* = k_1^*, K_2^* = k_2^*\Big) = \prod_{i=1}^{2}\binom{L_i}{k_i^*}p_i^{k_i^*}(1-p_i)^{L_i-k_i^*}. \qquad (2.12)$$

From equation (2.2) we see that,

$$\log\frac{p_1(1-p)}{p(1-p_1)} = -d\beta_1\Delta, \qquad (2.13)$$

i.e.,

$$p_1 = \frac{p(e^{-d\beta_1\Delta})}{1-p+p(e^{-d\beta_1\Delta})}. \qquad (2.14)$$

Similarly,

$$p_2 = \frac{p(e^{d\beta_2\Delta})}{1-p+p(e^{d\beta_2\Delta})}. \qquad (2.15)$$

Using equations (2.10), (2.11), (2.12), (2.14) and (2.15),

$$\begin{aligned}
&\frac{P_\Delta\left(K_1^* = k_1^*, K_2^* = k_2^*\right)}{P_0\left(K_1^* = k_1^*, K_2^* = k_2^*\right)} \\
&= \quad 1 + \Delta d\left[\left(\beta_2 k_2^* - \beta_1 k_1^*\right) - \left(L_2\beta_2 - L_1\beta_1\right)p\right] + \Delta o(1). \qquad (2.16)
\end{aligned}$$

By the results in equations (2.7) and (2.16), we can write equation (2.3) as:

$$\begin{aligned}
&\frac{P_{H_\Delta}(K_1^* = k_1^*, K_2^* = k_2^*, \boldsymbol{R} = \boldsymbol{r})}{P_{H_0}(K_1^* = k_1^*, K_2^* = k_2^*, \boldsymbol{R} = \boldsymbol{r})} \\
&= \quad 1 + \Delta c\Bigg[\sum_{i=1}^{k}\left(z_{(i)}c_i + \sum_{j=1}^{m_i} z_{ij}C_i\right) \\
&+ \quad \rho\Big\{(\beta_2 k_2^* - \beta_1 k_1^*) - (\beta_2 L_2 - \beta_1 L_1)p\Big\}\Bigg] + \Delta o(1), \qquad (2.17)
\end{aligned}$$

where $\rho = d/c$. Since the first term in (2.17) is a constant and the third term is negligible for small Δ, the LMPT statistic (see Randles & Wolfe 1991, page 295) for $H_0 : \Delta = 0$ versus $H_\Delta : \Delta > 0$, is the statistic in the brackets of (2.17), i.e.,

$$T = T_P + \rho T_B, \qquad (2.18)$$

where

$$T_P = \sum_{i=1}^{k}(z_{(i)}c_i + \sum_{j=1}^{m_i} z_{ij}C_i)$$

and

$$T_B = \Big\{(\beta_2 k_2^* - \beta_1 k_1^*) - (\beta_2 L_2 - \beta_1 L_1)p\Big\}.$$

Note that the LMPT is based on the number of responders k_1^*, k_1^* and the generalized rank vector $\boldsymbol{R}$. If we pick $\beta_1 = L_2/L$ and $\beta_2 = L_1/L$, then T_B takes the form

$$T_B = \frac{L_1 L_2}{L}\Big\{\frac{k_2^*}{L_2} - \frac{k_1^*}{L_1}\Big\}.$$

Hereafter, our test statistic will be referred to as T and is given by

$$\begin{aligned} T &= T_P + \rho T_B \\ &= \left[\sum_{i=1}^{k} \left(z_{(i)} c_i + \sum_{j=1}^{m_i} z_{ij} C_i \right) + \rho \frac{L_1 L_2}{L} \left\{ \frac{k_2^*}{L_2} - \frac{k_1^*}{L_1} \right\} \right], \end{aligned} \tag{2.19}$$

where $\rho = d/c$. Note that the locally most powerful test T for testing the hypothesis (2.1) versus (2.2) depends on ρ.

It is seen from the derivation that the test statistic does not depend on the choice of α. However, the choice of β affects the structure of the test statistic. There could be concern regarding the choice of β. Let us consider two different choices of β, namely (β_1, β_2) and (β_1', β_2'). We note that,

$$\begin{aligned} & T_B(\beta_1, \beta_2) - T_B(\beta_1', \beta_2') \\ &= \left\{ (\beta_2 k_2^* - \beta_1 k_1^*) - (\beta_2 L_2 - \beta_1 L_1) p \right\} - \left\{ (\beta_2' k_2^* - \beta_1' k_1^*) - (\beta_2' L_2 - \beta_1' L_1) p \right\} \\ &= (k_1^* - L_1 p)(\beta_1' - \beta_1) - (k_2^* - L_2 p)(\beta_2' - \beta_2) \\ &= (k^* - Lp)(\beta_1' - \beta_1). \end{aligned}$$

By choosing a different set of β, the difference in the test statistic in (2.18) is proportional to the difference between the total number of responders and the expected number (under H_0) of responders. If the consistent estimator $\hat{p} = k^*/L$ is substituted for p, then

$$T_B(\beta_1, \beta_2) - T_B(\beta_1', \beta_2') = 0.$$

Hence, it is reasonable to choose $\beta_1 = L_2/L$ and $\beta_2 = L_1/L$. When β_1 and β_2 are chosen as above then T_B is a test for comparing a difference of two proportions. Also, as shall be discussed in Chapter 3, this stucture is easily written in the stochastic integral form. Asymptotic properties are easily established.

CHAPTER 3
ASYMPTOTICS UNDER H_0

In this chapter we shall first introduce notation in terms of counting processes. Using the machinery available for counting processes we shall use the Martingale Central Limit Theorem to establish the large sample distribution of the statistic T given in equation (2.19).

3.1 Notation in Terms of Counting Processes

Let T_{ij} be the log-response-duration for subject j from group i, and let U_{ij} be the log-censoring time for subject j from group i, $i = 1,2; j = 1, \cdots, L_i$. Note that for nonresponders the log-response-duration is $-\infty$. If the censoring time is larger than the failure time then the failure time is observed, and hence is uncensored. If the censoring time is smaller than the failure time then we observe the censoring time, and label that observation as censored. Under the random censorship model, T_{ij} and U_{ij} are assumed to be independent. The available information on subject j from group i is the pair of random variables

$$X_{ij} = \min(T_{ij}, U_{ij}) \text{ and } \delta_{ij} = I\{X_{ij} = T_{ij}\},$$

where δ_{ij} is the censoring indicator.

It is assumed that all T_{ij}s and U_{ij}s are mutually independent and within group i, T_{ij}s and U_{ij}s are identically distributed with distribution functions

$$F_i(t) = P(T_{ij} \leq t) = 1 - P(T_{ij} > t) = 1 - S_i(t),$$

and

$$L_i^*(t) = P(U_{ij} \leq t) = 1 - P(U_{ij} > t) = 1 - C_i(t),$$

respectively, where S_i is the corresponding survival function and C_i is the corresponding censoring survival function. Let

$$\pi_i(t) = P(X_{ij} \geq t) = S_i(t)C_i(t),$$

and

$$N_{ij}(t) = I\{X_{ij} \leq t, \delta_{ij} = 1\}; \qquad N_i(t) = \sum_{j=1}^{L_i} N_{ij}(t); \qquad N(t) = \sum_{i=1}^{2} N_i(t).$$

be the counting processes that count the number of failures at or before log-time t for the j^{th} individual in group i, and in both groups, respectively, at or before log-time t. The corresponding counting processes for censored observations are:

$$N_{ij}^U(t) = I\{X_{ij} \leq t, \delta_{ij} = 0\}; \qquad N_i^U(t) = \sum_{j=1}^{L_i} N_{ij}^U(t); \qquad N^U(t) = \sum_{i=1}^{2} N_i^U(t).$$

Left-continuous processes Y that are the sizes of the risk sets just before time t are defined as follows:

$$Y_{ij}(t) = I\{X_{ij} \geq t\}; \qquad Y_i(t) = \sum_{j=1}^{L_i} Y_{ij}(t); \qquad Y(t) = \sum_{i=1}^{2} Y_i(t).$$

Hence, $Y_i(t)$ is the size of the risk set in group i at time $(t - 0)$. $Y(t)$ denotes the total size of the risk set at time $(t - 0)$.

The cumulative hazard function is defined as

$$\Lambda_i(t) = \int_{-\infty}^{t} \{1 - F_i(s-)\}^{-1} dF_i(s).$$

Note that this definition of $\Lambda_i(t)$ uses the left-continuous version of the distribution function. This facilitates handling tied observations.

3.2 Stochastic Integrals

In the previous chapter we have derived the structure of the LMPT. From the structure as given in equation (2.19) we see that our test statistic is:

$$T = \left[\ \sum_{i=1}^{k}\left(z_{(i)}c_i + \sum_{j=1}^{m_i} z_{ij}C_i\right) + \rho\frac{L_1L_2}{L}\left\{\frac{k_2^*}{L_2} - \frac{k_1^*}{L_1}\right\}\ \right]. \tag{3.1}$$

3.2.1 The Test Statistic T in the Stochastic Integral Form

We notice from the structure of equation (3.1) that our statistic is a linear combination of Prentice's (1978) statistic and a test for two sample proportions, or binomial test. Prentice and Marek (1979) and Mehrotra et al. (1982) have shown that Prentice's statistic can be written in terms of the observed number of failures and conditionally expected number of failures (conditional on the total size of the risk set). Andersen et al. (1982), page 234, have shown that such a statistic can be written as a Weighted Logrank Statistic in the counting processes framework. Specifically the test statistic in (3.1) is

$$T = \left[\int_{(-\infty,\infty]} \frac{Y_1(s)Y_2(s)}{Y}\left(\tilde{C}(s)-\tilde{c}(s)\right)\left(\frac{dN_1(s)}{Y_1(s)} - \frac{dN_2(s)}{Y_2(s)}\right)\right] + \rho\frac{L_1L_2}{L}\left\{\frac{k_2^*}{L_2} - \frac{k_1^*}{L_1}\right\}, \tag{3.2}$$

where $\tilde{c}(s)$ and $\tilde{C}(s)$ are the left continuous versions of Prentice's scores as mentioned in Prentice (1978) and Anderson et al. (1982). Observe that $N_i(-\infty)$ could be interpreted as the number of nonresponders in group i,$dN_i(-\infty) = L_i - k_i^*$. Also note that

$$\frac{dN_i(-\infty)}{Y_i(-\infty)} = \frac{L_i - k_i^*}{L_i},$$

$i = 1, 2$. Hence,

$$\frac{k_2^*}{L_2} - \frac{k_1^*}{L_1} = \frac{dN_1(-\infty)}{Y_1(-\infty)} - \frac{dN_2(-\infty)}{Y_2(-\infty)}.$$

Therefore the test statistic T takes the form:

$$T = \int_{[-\infty,\infty]} \frac{Y_1(s)Y_2(s)}{Y(s)} W(s) \left(\frac{dN_1(s)}{Y_1(s)} - \frac{dN_2(s)}{Y_2(s)} \right), \tag{3.3}$$

where

$$W(s) = \begin{cases} \tilde{C}(s) - \tilde{c}(s), & s > -\infty \\ \rho, & s = -\infty. \end{cases} \tag{3.4}$$

Note that $W(s)$ is an adapted, left-continuous process, i.e., predictable. Hence, the statistic T is a Weighted Logrank Statistic as discussed in Gill (1980), Andersen et al. (1982), Harrington and Fleming (1982), and Fleming and Harrington (1991).

3.2.2 Special Cases And Discussion

Special Cases

As given in equations (1.7), (1.8), (1.11), and (1.12), $(\tilde{C}(s) - \tilde{c}(s))$ has the form: for the logistic density,

$$\tilde{C}(s) - \tilde{c}(s) = \tilde{S}(s-)\frac{Y(s)}{Y(s)+1},$$

where $\tilde{S}(t) = \prod_{s \le t}\left(1 - \frac{dN(s)}{Y(s)+1}\right)$; for the Extreme Minimum Value density,

$$\tilde{C}(s) - \tilde{c}(s) \equiv 1.$$

If

$$\rho = \tilde{C}(-\infty) - \tilde{c}(-\infty)$$

then one could treat the nonresponders as responders, with response duration zero (uncensored), and perform a classical two-sample test for right censored data. Specifically,

1. In case the scores are generated from a logistic density and

$$\rho = \tilde{S}(-\infty-)\left(\frac{Y(-\infty)}{Y(-\infty)+1}\right) \approx 1,$$

   then the Peto & Peto (1972) test with nonresponders treated as responders is equivalent to performing the test based on T in (3.3). Hence, for a location shift alternative hypothesis with the underlying distribution of the data being logistic, the Peto & Peto (1972) test with pooling will result in a LMPT only if $\rho = 1$.

2. For scores generated from the extreme minimum value density, if

$$\rho = 1 = \tilde{C}(-\infty) - \tilde{c}(-\infty)$$

then the logrank test with nonresponders treated as responders is the same test as in (3.3). Of course, if $\rho \neq 1$ in reality then the logrank test with pooling will result in a loss in efficiency for the test.

3. As a special case if all subjects responded then it is easy to see that the second (binomial) component of the test statistic, T_B, will be zero and hence our combined test based on T is Prentice's (1978) test, a classical two-sample test with right censored data.

4. If all failures occured at one point, i.e., if all failures were tied at one failure time, then our test as given in equation (3.3) is a binomial test.

Discussion

1. Unidirectional Hypotheses

   The alternative hypothesis (2.2) on page 9 is an example of unidirectional hypothesis. Under hypothesis (2.2) the appropriate test is based on T as given in equation (2.19). Here it is clear that $S_2(t) \geq S_1(t)$. Consequently, the estimated cumulative hazard of group 1 is likely to be bigger than that of group 2. In other words it is likely that

$$\left(\frac{dN_1(s)}{Y_1(s)} - \frac{dN_2(s)}{Y_2(s)}\right) \geq 0.$$

   Moreover, since $p_2 \geq p_1$ the sign of T in equation (2.19) is likely to be positive.

2. Bidirectional Hypotheses

   Suppose now we are looking at a situation where the shifts in the rates and failure times are in opposite directions. For example, let us consider a cohort of Alzheimer's Disease patients. Let group I be the control group and group II be the treatment group. Suppose our interest is in reducing the rate of institutionalization in the treatment arm but expect distribution of survival times for those institutionalized in the treatment arm be longer. In this case the alternative hypothesis can be written as:

$$H_\Delta : \begin{cases} f_1(x) = f(x + c\alpha_1\Delta) \\ f_2(x) = f(x - c\alpha_2\Delta) \\ \log \frac{p_1(1-p)}{p(1-p_1)} = +d\beta_1\Delta \\ \log \frac{p_2(1-p)}{p(1-p_2)} = -d\beta_2\Delta \end{cases}, \tag{3.5}$$

   where all the parameters and constants in equation (3.5) have the same definitions as in equation (2.2). It is imperative to note that the test for the hypotheses (3.5) is no longer based on T; instead the appropriate test is now

based on

$$T_1 = \left[\int\limits_{(-\infty,\infty]} \frac{Y_1(s)Y_2(s)}{Y} \left(\tilde{C}(s) - \tilde{c}(s)\right) \left(\frac{dN_1(s)}{Y_1(s)} - \frac{dN_2(s)}{Y_2(s)} \right) \right] - \rho \frac{L_1 L_2}{L} \left\{ \frac{k_2^*}{L_2} - \frac{k_1^*}{L_1} \right\}. \tag{3.6}$$

However, it is now to be noted that

$$-\frac{L_1 L_2}{L} \left\{ \frac{k_2^*}{L_1} - \frac{k_1^*}{L_2} \right\} \neq \left(\frac{Y_1(-\infty)Y_2(-\infty)}{Y(-\infty)} \right) \left(\frac{dN_1(-\infty)}{Y_1(-\infty)} - \frac{dN_2(-\infty)}{Y_2(-\infty)} \right).$$

This fact does not in any way hinder our discourse on asymptotic normality, as we shall see in section (3.3). Furthermore it is clear that the asymptotic variance for our statistics for either hypotheses (2.2) or (3.5) will be unchanged.

Note that in this case when pooling, nonresponders must be treated as responders at time ∞ instead of at time 0, in order for the pooled tests to be comparable to the corresponding combined tests.

Issues regarding power of individual testing situations will be discussed in Chapter 5 through Monte Carlo simulation studies.

3.3 Weak Convergence of T_{PM} under H_0

In this section asymptotic normality of the test based on the statistic T given in equation (3.2) or (3.3) will be established. It should be noted that the first term in (3.2) is based on the response durations for the $k^*(=k_1^*+k_2^*)$ responders. Fleming and Harrington (1991), Corollary 7.2.1, page 260, give three conditions that are necessary for weak convergence of the weighted logrank statistic. Since the statistic T has a jump at $-\infty$, direct application of Corollary 7.2.1, Fleming and Harrington (1991) is justified through discussions in Helland (1982). Helland showed that any process that has a finite number of jumps in $[-\infty, log(t)]$ of sizes greater than $\varepsilon^* > 0$, can be handled by discretizing the process at the jump points. Discrete and continuous parts can be addressed separately.

Definition 3.1 Set $\mathcal{I} = \{t : \pi_1(t)\pi_2(t) > 0\}$.

Definition 3.2 Set $u = \sup\mathcal{I}$, so $u \notin \mathcal{I}$ when $u = \infty$. Denote $\tau \equiv \inf\{s : Y_1(s) \wedge Y_2(s) = 0\}$.

Consider the test based on the statistic given in equation (3.3). The normalized structure of the statistic is

$$T^*(\tau) = \left(\frac{L}{L_1L_2}\right)^{1/2} \int\limits_{[-\infty,\tau]} \frac{Y_1(s)Y_2(s)}{Y(s)} W(s)\left(\frac{dN_1(s)}{Y_1(s)} - \frac{dN_2(s)}{Y_2(s)}\right). \tag{3.7}$$

In proving weak convergence of the statistic given in equation (3.7) we will make the following assumption.

Assumption 3.1 For $i = 1, 2$ there exists a constant $a_i \in (0, 1)$ such that as $L \to \infty$

$$\frac{L_i}{L} \to a_i.$$

The following Lemma can be shown by arguments in the proof of theorem 5.5.1, page 133, Chung (1974).

Lemma 3.1 For the empirical estimator $\frac{Y_i(t)}{L_i}$ of $\pi_i(t)$,

$$\sup_{-\infty \leq t < \infty} \left| \frac{Y_i(t)}{L_i} - \pi_i(t) \right| \xrightarrow{P} 0.$$

The following theorem is a modified version of Corollary 7.2.1, Fleming and Harrington (1991), page 260.

Theorem 3.1 Suppose $F_1 = F_2 = F$. Let

$$K(s) = \left(\frac{L}{L_1 L_2}\right)^{1/2} \frac{Y_1(s) Y_2(s)}{Y(s)} W(s). \tag{3.8}$$

Suppose that:

1.

$$\frac{K^2(s)}{Y_i(s)} \xrightarrow{P} h_i(s)$$

uniformly on $[-\infty, t]$ for any $t \in \mathcal{I}$ as $L \to \infty$, where h_i is a nonnegative, left-continuous function with right hand limits such that $h_i(t) < \infty$ and h_i^+, the right-continuous adaptation of h_i on the interval $\mathcal{I}$, is of bounded variation on each closed subinterval of $\mathcal{I}$, and $h_i(t) = 0$ for any $t \notin \mathcal{I}$.

2. If $u \notin \mathcal{I}$, assume

(a)

$$\sigma^2(u) = \int_{[-\infty,u]} \Big(h_1(s) + h_2(s)\Big)\Big(1 - \Delta\Lambda(s)\Big) d\Lambda(s) < \infty$$

and

(b) for any $\varepsilon > 0$,

$$\lim_{t \uparrow u} \limsup_{L \to \infty} P\Big\{ \int_{[t,u]} K^2(s) \frac{Y(s)}{Y_1(s) Y_2(s)} d\Lambda(s) > \varepsilon \Big\} = 0.$$

3. In addition, if $u < \infty$,

$$\lim_{L\to\infty} P\Big\{ \int_{[u,\infty]} K^2(s)\frac{Y(s)}{Y_1(s)Y_2(s)}d\Lambda(s) > \varepsilon\Big\} = 0,$$

for any $\varepsilon > 0$.

Let

$$\hat{\sigma}_1^2(t) = \int_{[-\infty,t]} K^2(s)\Big(\frac{Y(s)}{Y_1(s)Y_2(s)}\Big)\Big(1 - \frac{\Delta N(s) - 1}{Y(s) - 1}\Big)\frac{dN(s)}{Y(s)} \tag{3.9}$$

and

$$\hat{\sigma}_2^2(t) = \sum_{i=1}^{2} \int_{[-\infty,t]} \frac{K^2(s)}{Y_i(s)}\Big(1 - \frac{\Delta N_i(s) - 1}{Y_i(s) - 1}\Big)\frac{dN_i(s)}{Y_i(s)}. \tag{3.10}$$

Then, as $L \to \infty$, for any $\tau \in [-\infty, \infty]$,

$$\frac{T^*(\tau)}{\{\hat{\sigma}_i^2(\tau)\}^{1/2}} \xrightarrow{D} N(0,1).$$

The estimators in (3.9) and (3.10) are quoted from equations (4.1.21) and (4.1.20) on page 58, Gill (1980). These estimators are shown to be consistent estimators for

$$\sigma^2(\tau) = \int_{[-\infty,\tau]} \frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}k^2(t)(1 - \Delta\Lambda(t))d\Lambda(t). \tag{3.11}$$

Note that

$$h_1(s) + h_2(s) = \frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}k^2(t).$$

Conditions of theorem 3.1 will be verified to establish the weak convergence of T^* with scores generated from logistic and extreme minimum value densities. In both cases, the weight function $W(s)$ is discontinuous at $t = -\infty$. Hence in checking the

conditions in theorem 3.1 the cases $t > -\infty$ and $t = -\infty$ will be addressed separately. From equation (3.8) it is clear that for logistic density

$$K(t) = K_{PP}(t) = \begin{cases} \left(\frac{L_1 L_2}{L}\right)^{1/2} \left\{\tilde{S}(t-)\frac{Y(t)}{Y(t)+1}\right\} \left(\frac{Y_1(t)}{L_1}\right)\left(\frac{Y_2(t)}{L_2}\right)\left(\frac{L}{Y(t)}\right), & t > -\infty \\ \left(\frac{L_1 L_2}{L}\right)^{1/2} \rho, & t = -\infty. \end{cases} \tag{3.12}$$

When the scores are generated from extreme minimum value density,

$$K(t) = K_{L}(t) = \begin{cases} \left(\frac{L_1 L_2}{L}\right)^{1/2} \left(\frac{Y_1(t)}{L_1}\right)\left(\frac{Y_2(t)}{L_2}\right)\left(\frac{L}{Y(t)}\right), & t > -\infty \\ \left(\frac{L_1 L_2}{L}\right)^{1/2} \rho, & t = -\infty. \end{cases} \tag{3.13}$$

Weak convergence will be shown only for T_{PP}. The arguments for T_L are similar to those for T_{PP} and shall be omitted.

3.3.1 Weak Convergence of Peto & Peto (1972)'s Version of Equation (3.3).

Arguments verifying the conditions of theorem 3.1 will follow those given in Fleming & Harrington (1991) pages 261-263.

For $t > -\infty$

For responders,

$$\frac{K_{PP}^2(t)}{Y_i(t)} = \frac{L}{L_1L_2}\Big(\frac{Y_1(t)Y_2(t)}{Y(t)}\Big)^2\Big[\hat{S}(t-)\frac{Y(t)}{Y(t)+1}\Big]^2\frac{1}{Y_i(t)}. \tag{3.14}$$

By assumption (3.1) and lemma (3.1), it is concluded that $\frac{K_{PP}^2(t)}{Y_i(t)} \xrightarrow{P} h_i(t)$ uniformly on $(-\infty, t]$ for any $t \in \mathcal{I}$ as $L \to \infty$, where

$$h_i(t) = a_{(3-i)}\big\{S(t-)\big\}^2\frac{\pi_1^2(t)\pi_2^2(t)}{\pi_i(t)\big(a_1\pi_1(t)+a_2\pi_2(t)\big)^2} < \infty.$$

Condition (1) of theorem (3.1) is satisfied.

Note,

$$\Delta\Lambda(t) = \frac{\Delta F(t)}{1-F(t-)} = \frac{F(t)-F(t-)}{1-F(t-)}.$$

Hence,

$$1-\Delta\Lambda(t) = \frac{1-F(t)}{1-F(t-)} \le 1,$$

which implies that

$$\int_{(-\infty,u]} h_i(1-\Delta\Lambda)d\Lambda \le \int_{(-\infty,u]} h_i d\Lambda \le \int_{(-\infty,u]} (h_1+h_2)d\Lambda. \tag{3.15}$$

For condition (2a), using equations (3.15), we see

$$\int_{(-\infty,u]} h_i(1-\Delta\Lambda)d\Lambda$$

$$
\begin{aligned}
&\leq \int_{(-\infty,u]} (h_1 + h_2) d\Lambda \\
&= \int_{(-\infty,u]} \Big(S(s-)\Big)^2 \left(\frac{\pi_1\pi_2}{a_1\pi_1 + a_2\pi_2}\right) d\Lambda \\
&\leq \int_{(-\infty,u]} \frac{\pi_1}{a_2} d\Lambda \\
&\leq \frac{1}{a_2} \int_{(-\infty,u]} S(s-) d\Lambda \\
&< \frac{1}{a_2} \\
&< \infty. \qquad (3.16)
\end{aligned}
$$

Hence $\sigma^2(u) < \infty$, i.e., condition (2a) is satisfied.

Condition (2b) follows by following arguments in lemma 7.2.2 of Fleming and Harrington (1991). Note that,

$$
\begin{aligned}
&K^2_{PP}(t)\frac{Y(t)}{Y_1(t)Y_2(t)} \\
&= \left(\frac{L}{L_1L_2}\right)\left(\tilde{S}(t-)\frac{Y(t)}{Y(t)+1}\right)^2\left(\frac{Y_1(t)Y_2(t)}{Y(t)}\right) \\
&\leq \frac{L}{L_{(3-i)}}\left(\frac{Y_i(t)}{L_i}\right).
\end{aligned}
$$

Since $a_{(3-i)} > 0$, lemma 7.2.2 of Fleming & Harrington (1991) and assumption (3.1) implies

$$
\int_{(t,u]} \frac{L}{L_{(3-i)}}\left(\frac{Y_i}{L_i}\right) d\Lambda \xrightarrow{P} \frac{1}{a_{(3-i)}} \int_{(t,u]} \pi_i d\Lambda.
$$

The condition (2b) follows immediately if $\Delta\Lambda(u) = 0$. Since $u \notin \mathcal{I}$, we can assume $\pi_i(u) = 0$. If $\Delta\Lambda(u) > 0$, the condition is satisfied, since $a_{(3-i)} > 0$ and $\pi_i(u) = 0$ and

hence

$$\int_{\{u\}} \frac{L}{L_{(3-i)}} \left(\frac{Y_i}{L_i} \right) d\Lambda \xrightarrow{P} 0.$$

Condition (3) is satisfied since lemma 7.2.2 of Fleming and Harrington (1991) implies that,

$$\int_{[u,\infty]} \frac{L}{L_{(3-i)}} \left(\frac{Y_i}{L_i} \right) d\Lambda \xrightarrow{P} \frac{1}{a_{(3-i)}} \int_{[u,\infty]} \pi_i d\Lambda.$$

<u>For $t = -\infty$.</u>

Since $Y_i(t)$ is the size of the risk set in group i at $t-$, $Y_i(-\infty) = L_i$, and $Y(-\infty) = L$. The cumulative hazard function

$$\Lambda(t) = \int_{-\infty}^{t} \{1 - F(s-)\}^{-1} dF(s)$$

$$\Rightarrow \quad \Delta\Lambda(t) = \{1 - F(t-)\}^{-1} \Delta F(t)$$

$$\Rightarrow \quad \Delta\Lambda(-\infty) = \frac{F(-\infty) - F(-\infty-)}{1 - F(-\infty-)} = F(-\infty) = p.$$

Since

$$K_{PP}(-\infty) = \left(\frac{L_1 L_2}{L} \right)^{1/2} (\rho),$$

clearly

$$\frac{K_{PP}^2(-\infty)}{Y_i(-\infty)} = \left(\frac{L_1 L_2}{L} \right) \rho^2 \frac{1}{L_i} = \left(\frac{L_{(3-i)}}{L} \right) \rho^2.$$

Under assumption (3.1), as $L \to \infty$,

$$\frac{K_{PP}^2(-\infty)}{Y_i(-\infty)} \xrightarrow{P} h_i(-\infty),$$

where $h_i(-\infty) = \rho^2 a_{(3-i)} < \infty$. Hence, h_i is a non-negative constant (and hence left-continuous, with right-hand limits), and $h_i < \infty$. Condition (1) of theorem (3.1) is satisfied. Now,

$$\Big\{h_1(-\infty) + h_2(-\infty)\Big\}\Big(1 - \Delta\Lambda(-\infty)\Big)\Delta\Lambda(-\infty) = p(1-p)\rho^2 < \infty. \tag{3.17}$$

Hence, condition (2a) of theorem (3.1) is satisfied.

At $s = -\infty$ conditions (2b) and (3) of theorem 3.1 is vacuous and hence does not need to be addressed.

Since the conditions of theorem 3.1 are satisfied, for any $\tau \in [-\infty, \infty]$,

$$\frac{T^\star_{PP}(\tau)}{\{\sigma^2(\tau)\}^{1/2}} \xrightarrow{D} N(0,1),$$

and similarly

$$\frac{T^\star_{L}(\tau)}{\{\sigma^2(\tau)\}^{1/2}} \xrightarrow{D} N(0,1).$$

The appropriate variances are $\sigma^2_{PP}(\tau)$ and $\sigma^2_L(\tau)$, respectively, defined below.

For the purpose of deriving asymptotic relative efficiency in Chapter 4, $\sigma^2(\tau)$ can be expressed as

$$\sigma^2(\tau) = \int\limits_{(-\infty,\tau]} \Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\Big) k^2(t)(1 - \Delta\Lambda(t))d\Lambda(t) + \rho^2 p(1-p), \tag{3.18}$$

where

$$k^2(t) = \lim_{l\to\infty} \Big(\frac{L}{L_1L_2}\Big) K^2(t),$$

uniformly in probability on each closed sub-interval of $\mathcal{I}$.

For special cases $T^\star_{PP}$ and $T^\star_L$, the corresponding $k^2(t)$'s are

$$k^2_{PP}(t) = \begin{cases} \Big\{S(t-)\Big\}^2 \Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_2(t)+a_2\pi_2(t)}\Big), & t > -\infty \\ \rho, & t = -\infty \end{cases} \tag{3.19}$$

and

$$k_L^2(t) = \begin{cases} \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_2(t)+a_2\pi_2(t)}\right), & t > -\infty \\ \rho, & t = -\infty, \end{cases} \tag{3.20}$$

respectively.

According to the structure of $\sigma^2(\tau)$ in (3.18), using (3.19) and (3.20), the asymptotic variances of $T_{PP}^\star(\tau)$ and $T_L^\star(\tau)$ have the forms

$$\sigma_{PP}^2(\tau) = \int_{(-\infty,\tau]} \left[\tilde{S}(t)\right]^2 \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)\left(1 - \Delta\Lambda(t)\right) d\Lambda(t) + \rho^2 p(1-p) \tag{3.21}$$

and

$$\sigma_L^2(\tau) = \int_{(-\infty,\tau]} \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)\left(1 - \Delta\Lambda(t)\right) d\Lambda(t) + \rho^2 p(1-p), \tag{3.22}$$

respectively.

Estimators for $\sigma^2(\tau)$ for the statistic $T_{PP}^\star$ and $T_L^\star$ are given below.

Based on equation (3.9) and (3.12), for Peto & Peto's version of the statistic,

$$\hat{\sigma}^2_{1PP}(t)$$

$$= \int_{(-\infty,t]} \left\{\left(\frac{L_1L_2}{L}\right)^{1/2}\left((\tilde{S}-)\frac{Y}{Y+1}\right)\frac{Y_1}{L_1}\frac{Y_2}{L_2}\frac{L}{Y}\right\}^2\left(\frac{Y}{Y_1Y_2}\right)\left(1-\frac{\Delta N-1}{Y-1}\right)\frac{dN}{Y}$$

$$+ \left\{\left(\frac{L_1L_2}{L}\right)^{1/2}(\rho)\right\}^2\left(\frac{Y(-\infty)}{Y_1(-\infty)Y_2(-\infty)}\right)\left(1-\frac{\Delta N(-\infty)-1}{Y(-\infty)-1}\right)\frac{\Delta N(-\infty)}{Y(-\infty)}$$

$$= \int_{(-\infty,t]} \left\{(\tilde{S}-)\right\}^2\frac{L}{L_1L_2}\frac{Y_1Y_2Y}{(Y+1)^2}\left(1-\frac{\Delta N-1}{Y-1}\right)\frac{dN}{Y}$$

$$+ \rho^2\frac{k^*(L-k^*)}{L(L-1)}, \tag{3.23}$$

and, based on equation (3.10) and (3.12),

$$\hat{\sigma}^2_{2PP}(t)$$

$$= \sum_{i=1}^{2}\Bigg[\int_{(-\infty,t]} \left\{\left(\frac{L_1L_2}{L}\right)^{1/2}\left((\tilde{S}-)\frac{Y}{Y+1}\right)\frac{Y_1}{L_1}\frac{Y_2}{L_2}\frac{L}{Y}\right\}^2\frac{1}{Y_i}\left(1-\frac{\Delta N_i-1}{Y_i-1}\right)\frac{dN_i}{Y_i}$$

$$+ \left\{\left(\frac{L_1L_2}{L}\right)^{1/2}(\rho)\right\}^2\frac{1}{Y_i(-\infty)}\left(1-\frac{\Delta N_i(-\infty)-1}{Y_i(-\infty)-1}\right)\frac{\Delta N_i(-\infty)}{Y_i(-\infty)}\Bigg]$$

$$= \sum_{i=1}^{2}\Bigg[\int_{(-\infty,t]} \left((\tilde{S}-)\right)^2\frac{L}{L_1L_2}\frac{Y_1^2Y_2^2}{Y_i(Y+1)^2}\left(1-\frac{\Delta N_i-1}{Y_i-1}\right)\frac{dN_i}{Y_i}$$

$$+ \rho^2\frac{L_{(3-i)}}{L}\frac{k_i^*(L_i-k_i^*)}{L_i(L_i-1)}\Bigg]. \tag{3.24}$$

Based on equation (3.9) and (3.13), for logrank version of the statistic,

$$
\begin{aligned}
&\hat{\sigma}^2_{1L}(t)\\
= & \int_{(-\infty,t]} \left\{ \left(\frac{L_1L_2}{L}\right)^{1/2} \frac{Y_1(t)}{L_1}\frac{Y_2(t)}{L_2}\frac{L}{Y(t)} \right\}^2 \left(\frac{Y}{Y_1Y_2}\right)\left(1-\frac{\Delta N - 1}{Y-1}\right)\frac{dN}{Y}\\
+ & \left\{ \left(\frac{L_1L_2}{L}\right)^{1/2} (\rho) \right\}^2 \left(\frac{Y(-\infty)}{Y_1(-\infty)Y_2(-\infty)}\right)\left(1-\frac{\Delta N(-\infty) - 1}{Y(-\infty)-1}\right)\frac{\Delta N(-\infty)}{Y(-\infty)}
\end{aligned}
$$

$$
\begin{aligned}
= & \int_{(-\infty,t]} \frac{L}{L_1L_2}\frac{Y_1Y_2}{Y}\left(1-\frac{\Delta N - 1}{Y-1}\right)\frac{dN}{Y}\\
+ & \rho^2 \frac{k^*(L-k^*)}{L(L-1)}, \qquad (3.25)
\end{aligned}
$$

and, based on equation (3.10) and (3.13),

$$
\begin{aligned}
&\hat{\sigma}^2_{2L}(t)\\
= & \sum_{i=1}^{2} \Bigg[\int_{(-\infty,t]} \left\{ \left(\frac{L_1L_2}{L}\right)^{1/2} \frac{Y_1(t)}{L_1}\frac{Y_2(t)}{L_2}\frac{L}{Y(t)} \right\}^2 \frac{1}{Y_i}\left(1-\frac{\Delta N_i - 1}{Y_i-1}\right)\frac{dN_i}{Y_i}\\
+ & \left\{ \left(\frac{L_1L_2}{L}\right)^{1/2} (\rho) \right\}^2 \frac{1}{Y_i(-\infty)}\left(1-\frac{\Delta N_i(-\infty) - 1}{Y_i(-\infty)-1}\right)\frac{\Delta N_i(-\infty)}{Y_i(-\infty)} \Bigg]
\end{aligned}
$$

$$
\begin{aligned}
= & \sum_{i=1}^{2} \Bigg[\int_{(-\infty,t]} \frac{L}{L_1L_2}\frac{Y_1^2Y_2^2}{Y^2}\frac{1}{Y_i}\left(1-\frac{\Delta N_i - 1}{Y_i-1}\right)\frac{dN_i}{Y_i}\\
+ & \rho^2 \frac{L_{(3-i)}}{L}\frac{k_i^*(L_i-k_i^*)}{L_i(L_i-1)} \Bigg]. \qquad (3.26)
\end{aligned}
$$

In our computations during Monte Carlo simulations in Chapter 5 we will use equations (3.23) and (3.25) as the variance estimates for the Peto & Peto and the logrank versions of our test statistic $T^{\star}$.

CHAPTER 4
ASYMPTOTICS UNDER H_Δ

4.1 Introduction

Weighted logrank tests are consistent against ordered hazards and stochastic ordering alternatives, as shown in Fleming & Harrington (1991), pages 265-267. Such tests have powers converging to unity as the sample size goes to ∞ for any fixed alternative of these two types. As a result, a more refined measure of the asymptotic operating characteristic must be used to discriminate among tests. The concept of asymptotic relative efficiency plays a central role in the asymptotic theory of hypothesis testing, and is discussed in the context of nonparametric tests by Randles & Wolfe (1991). The underlying idea involves a contiguous sequence of alternative hypotheses converging to the null hypothesis (Andersen et al. 1993, and, Fleming and Harrington 1991) at the "right" rate, as the sample size goes to ∞. Under such a sequence the distribution of the statistic has, asymptotically, a finite mean and a positive variance. The asymptotic distribution under the contiguous sequence of alternatives then provides approximate operating characteristics of a test in large samples and for local alternatives, i.e., alternatives "close" to the null hypothesis. For our purpose in this chapter we shall consider a sequence of alternatives, in (2.2), depending on

$$\Delta^L = \frac{1}{\sqrt{L}}. \tag{4.1}$$

This choice of a sequence of local alternatives has been used by authors in the uncensored data case (Johnson et al. 1987).

4.2 The Weighted Logrank Statistic

For notational clarity, let p_i^L, f_i^L, F_i^L, S_i^L, λ_i^L, and Λ_i^L be the proportion of responders, density function, distribution function, survival function, hazard function and cumulative hazard function respectively under the alternative hypothesis H_{Δ^L} for group $i = 1, 2$. Let K^L be the weight function in (3.8), which depends on L. Also, as defined in chapter 3, let Λ be the cumulative hazard function under the null hypothesis. Of course, under the sequence of contiguous alternatives Λ is the limiting value of Λ_i^L as $L \to \infty$. We have shown in Chapters 2 and 3 that a weighted logrank test is locally most powerful if the weight function K^L is constructed from the underlying distribution of the data under H_0. Pitman's ARE is related to misspecification of the weight function $K^L(t)$ including possible misspecification of ρ. For detailed information on ARE, readers are referred to Randles & Wolfe (1991). In this chapter the statistic T^* will be written as $T(t, K^L)$, given by

$$T(t, K^L) = \int_{[-\infty,t]} \frac{K^L(s)}{Y_1(s)} dN_1(s) - \int_{[-\infty,t]} \frac{K^L(s)}{Y_2(s)} dN_2(s). \tag{4.2}$$

Let

$$M_i^L(t) = N_i(t) - \int_{[-\infty,t]} Y_i(s) d\Lambda_i^L(s) \tag{4.3}$$

be the Martingale processes for group i. Now using the compensators $\int_{[-\infty,t]} Y_i(s) d\Lambda_i^L(s)$ for the counting processes N_i, $i = 1, 2$, we see that

$$T(t, K^L) = \int_{[-\infty,t]} \frac{K^L(s)}{Y_1(s)} dM_1^L(s) - \int_{[-\infty,t]} \frac{K^L(s)}{Y_2(s)} dM_2^L(s)$$

$$+ \int_{[-\infty,t]} K^L(s) \Big(\frac{d\Lambda_1^L(s)}{d\Lambda(s)} - 1 \Big) d\Lambda(s)$$

$$- \int_{[-\infty,t]} K(s)\Big(\frac{d\Lambda_2^L(s)}{d\Lambda(s)} - 1\Big) d\Lambda(s). \tag{4.4}$$

The structure of $T(t, K^L)$ in equation (4.4) will be useful in the derivation of the efficacy formulæ and Pitman's ARE.

4.3 Asymptotics Under a Sequence of Alternatives

In chapter 3 of this manuscript , sufficient conditions for a limiting null distribution were stated and verified for $T(\infty, K^L)$, as given in equation (4.2). Gill (1980) gave sufficient conditions for asymptotic normality of the weighted logrank test under a contiguous sequence of alternative hypotheses. Quoted by Fleming & Harrington (1991) in theorem 7.4.1, page 269, these conditions are listed below in theorem 4.1. We verify these conditions in section 4.4 for the test statistics $T(\infty, K^L)$ under the sequence of alternative hypotheses described in section 4.1.

Theorem 4.1 Consider the statistic $T(t, K^L)$ in equation (4.2). In addition to assumption 3.1, suppose that for $i = 1, 2$, each of the following conditions is satisfied:

1. For a distribution function, F, with respect to which each F_i^L is absolutely continuous,

$$\sup_{-\infty \leq t < \infty} |F_i^L(t) - F(t)| \to 0 \text{ as } L \to \infty. \tag{4.5}$$

There exists a real valued function γ_i such that

$$\left(\frac{L_1 L_2}{L}\right)^{1/2} \left(\frac{d\Lambda_i^L}{d\Lambda}(t) - 1\right) \to \gamma_i(t) \text{ as } L \to \infty \tag{4.6}$$

uniformly on each closed subinterval of $\{t : F(t-) < 1\}$ and

$$\int_{[-\infty,t]} |\gamma_i| d\Lambda < \infty \text{ for all } t \in \mathcal{I},\ i = 1, 2. \tag{4.7}$$

There exists a left-continuous function θ, with right-hand limits θ^+ of bounded variation on closed subintervals of $\mathcal{I}$, and $\theta = 0$ outside $\mathcal{I}$, such that

$$\left(\frac{L}{L_1 L_2}\right)^{1/2} K^L(t) \to \theta(t) \text{ as } L \to \infty \tag{4.8}$$

uniformly in probablity on a closed subinterval of $\mathcal{I}$.

Then as $L \to \infty$ and $\forall t \in \mathcal{I}$,

$$T(t, K^L) \xrightarrow{D} N(\mu(t), \sigma^2(t)), \tag{4.9}$$

where

$$\mu(t) = \int_{[-\infty,t]} \theta(s)\gamma(s)d\Lambda(s), \tag{4.10}$$

with $\gamma(s) = \gamma_1(s) - \gamma_2(s)$, and

$$\sigma^2(t) = \int_{[-\infty,t]} \frac{(a_1\pi_1(s) + a_2\pi_2(s))}{\pi_1(s)\pi_2(s)}\theta^2(s)\big(1 - \Delta\Lambda(s)\big)d\Lambda(s). \tag{4.11}$$

If $\hat{\sigma}^2(t)$ is defined in equations (3.9) and (3.10), then

$$\hat{\sigma}^2(t) \xrightarrow{P} \sigma^2(t). \tag{4.12}$$

2. If $u \notin \mathcal{I}$, assuming

a) For $i = 1, 2$,

$$\lim_{t \uparrow u} \limsup_{L\to\infty} \sup_{s\in(t,u]} \left|\frac{d\Lambda_i^L}{d\Lambda_{3-i}^L}(s)\right| < \infty; \tag{4.13}$$

b) For $h_i(t)$ defined in condition (1) on page 24

$$\int_{\mathcal{I}} h_i(1 - \Delta\Lambda_i)d\Lambda_i < \infty. \tag{4.14}$$

c) For any $\varepsilon > 0$ and $i = 1, 2$

$$\lim_{t\uparrow u} \limsup_{L\to\infty} P\Big\{ \int_{[t,u]} \frac{\{K^L\}^2}{Y_i} d\Lambda_i^L > \varepsilon \Big\} = 0. \tag{4.15}$$

d)

$$\int_{\mathcal{I}} |\theta\gamma_i| d\Lambda < \infty;$$

e)

$$\lim_{t \uparrow u} \limsup_{L \to \infty} P\left\{ \int_{t-}^{u} |K^L||d\Lambda_i^L - d\Lambda| > \varepsilon \right\} = 0 \text{ for any } \varepsilon > 0; \tag{4.16}$$

then as $L \to \infty$, (4.9) and (4.12) also hold for $t = u$.

3. If $u < \infty$, assuming

a) For $i = 1, 2$,

$$\limsup_{L \to \infty} \sup_{s \in (t,u]} \left| \frac{d\Lambda_i^L}{d\Lambda_{3-i}^L}(s) \right| < \infty; \tag{4.17}$$

b) As $L \to \infty$,

$$\int_{[u,\infty]} \frac{\{K^L\}^2}{Y_i} d\Lambda_i^L \xrightarrow{P} 0. \tag{4.18}$$

c)

$$\int_{[u,\infty]} |K^L||d\Lambda_i^L - d\Lambda| \xrightarrow{P} 0 \text{ as } L \to \infty; \tag{4.19}$$

then, as $L \to \infty$, equations (4.9) and (4.12) also hold for any $t \in [-\infty, \infty]$.

4.4 Verification of Gill's (1980) Sufficient Conditions

In this section we will verify the smoothness conditions stated in theorem 4.1 for the statistic (4.2). The arguments that follow will be applied to the logistic and the extreme minimum value densities. The logistic density and its corresponding hazard function is

$$f(t) = e^t(1+e^t)^{-2}, \qquad -\infty < t < \infty, \tag{4.20}$$

and

$$\lambda(t) = \frac{e^t}{1+e^t}, \tag{4.21}$$

respectively. The extreme minimum value density and its corresponding hazard function is

$$f(t) = e^{(t-e^t)}, \qquad -\infty < t < \infty, \tag{4.22}$$

and

$$\lambda(t) = e^t, \tag{4.23}$$

respectively. Note that both logistic and the extreme minimum value densities are absolutely continuous. We assume that the density function f in (2.1) has smooth first derivatives and the corresponding hazard function λ is positive on $\mathcal{I}$. The following additional assumptions are made in subsequent arguments in this chapter.

Assumption 4.1 There exists a constant Q, such that

$$\left|\frac{\lambda'(t)}{\lambda(t)}\right| < Q, \text{ uniformly for } t \text{ on } \mathcal{I}.$$

Assumption 4.2 There exists positive constants Q_2, $L' < u$ and δ, such that, for $t \in (L', u)$ and $\left|\theta\right| < \delta$,

$$\left|\frac{\lambda(t+\theta)}{\lambda(t)}\right| < Q_2.$$

It is easy to see that the assumptions (4.1) and (4.2) are satisfied for the logistic and the extreme minimum value densities.

In order to verify the conditions given in theorem 4.1 a mixture density is introduced below.

The Mixture Density

Based on the definition of X_{ij} in chapter 3, the underlying density for the random variable X_{ij} is

$$g_i^L(x) = (1 - p_i^L)I_{\{x=-\infty\}} + p_i^L f_i^L(x)I_{\{x>-\infty\}}, \tag{4.24}$$

under $H_\Delta : \Delta^L > 0$. Under $H_0 : \Delta^L = 0$, the density function of X_{ij} is

$$g(x) = (1 - p)I_{\{x=-\infty\}} + pf(x)I_{\{x>-\infty\}}. \tag{4.25}$$

Since g is a mixture density we can write the corresponding hazard function as a sum of the discrete and the continuous parts. That is, we write

$$\lambda_i^L(x) = \lambda_{i(cont)}^L(x) + \lambda_{i(discrete)}^L(x), \ i = 1, 2.$$

Under H_0, we also express

$$\lambda(x) = \lambda_{(cont)}(x) + \lambda_{(discrete)}(x).$$

Clearly, the pieces for the above are:

$$\lambda_{i(discrete)}^L(-\infty) = 1 - p_i^L,$$

$$\lambda_{i(cont)}^L(x) = \frac{f_i^L(x)}{1 - F_i^L(x)},$$

$$\lambda_{(discrete)}(-\infty) = 1 - p,$$

$$\lambda_{(cont)}(x) = \frac{f(x)}{1 - F(x)},$$

and $\lambda^L_{i(discrete)}(x) = \lambda_{(discrete)}(x) = 0$ for $x > -\infty$. For $i = 1, 2$, the cumulative hazards, under H_Δ and H_0, can respectively be written as

$$\Lambda^L_i(x) = \Lambda^L_{i(cont)}(x) + (1 - p^L_i) \tag{4.26}$$

and

$$\Lambda(x) = \Lambda_{(cont)}(x) + (1 - p),$$

where $\Lambda^L_{i(cont)}(x) = \int\limits_{(-\infty,x)} \lambda^L_{i(cont)}(t)dt$, and $\Lambda_{(cont)}(t)$ is similarly defined. Then it is clear that for $x > -\infty$,

$$d\Lambda^L_i(x) = d\Lambda^L_{i(cont)}(x) = \lambda^L_{i(cont)}(x)dx, \tag{4.27}$$

$$d\Lambda(x) = d\Lambda_{(cont)}(x) = \lambda_{(cont)}(x)dx, \tag{4.28}$$

and

$$\Delta\Lambda^L_i(-\infty) = 1 - p^L_i, \quad \Delta\Lambda(-\infty) = 1 - p. \tag{4.29}$$

In the test statistic (4.2), the weight function $K^L(t)$ (with $K^L(t) = K^L_{PP}(t)$ for Peto & Peto (1972), in (3.12), and $K^L(t) = K^L_L(t)$ for logrank, in (3.13)) involves ρ. Usually, ρ is an unknown parameter. In practice, one may misspecify ρ in (4.2). In order to evaluate the loss in efficiency by misspecifying ρ, we assume that a value ρ_1, instead of the true value of ρ, has been used in K^L_{PP}, and K^L_L. The density function from which scores are generated may be different from the underlying density also. The verification of conditions in theorem 4.1 for the statistics $T(\infty, K_{PP})$ and $T(\infty, K_L)$ will be done for the cases $t = -\infty$ and $t > -\infty$ separately.

<u>Case 1: $t = -\infty$</u>

For Peto & Peto and logrank tests, $\theta(-\infty)$ takes the form:

$$\begin{aligned}
&\theta(-\infty) \\
&= \lim_{L\to\infty}\left(\frac{L}{L_1L_2}\right)^{1/2} K^L(-\infty) \\
&= \rho_1 \\
&= \theta_{PP}(-\infty) = \theta_L(-\infty).
\end{aligned} \tag{4.30}$$

Note also that

$$\begin{aligned}
&\gamma_1(-\infty) \\
&= \lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\frac{\Delta\Lambda_1^L(-\infty)}{\Delta\Lambda(-\infty)} - 1\right\} \\
&= \lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\frac{1-p_1^L}{1-p} - 1\right\} \\
&= \lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\frac{1}{1-p(1-e^{-d\beta_1\Delta^L})} - 1\right\} \\
&= \lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\frac{1-1+p(1-e^{-d\beta_1\Delta^L})}{1-p(1-e^{-d\beta_1\Delta^L})}\right\} \\
&= p\lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\frac{(d\beta_1\Delta^L)}{(1-pd\beta_1\Delta^L)}.
\end{aligned} \tag{4.31}$$

Taylor's expansion of $(1-e^{-d\beta_1\Delta^L})$ around $\Delta^L = 0$ was used in (4.31). Using equation (4.1), and assumption 3.1 and substituting $\beta_1 = L_2/L$, we have from equation (4.31),

$$\begin{aligned}
&\gamma_1(-\infty) \\
&= pd \lim_{L\to\infty}\left(\frac{L_1}{L}\right)^{1/2}\left(\frac{L_2}{L}\right)^{1/2}\left(\frac{L_2}{L}\right)\left(\frac{1}{1-pd\frac{L_2}{L}\frac{1}{L^{1/2}}}\right) \\
&= pda_1^{1/2}a_2^{3/2}.
\end{aligned} \tag{4.32}$$

Similarly, it follows that

$$\begin{aligned}
&\gamma_2(-\infty) \\
&= \quad -pd \quad \lim_{L\to\infty}\left(\frac{L_1}{L}\right)^{1/2}\left(\frac{L_2}{L}\right)^{1/2}\left(\frac{L_1}{L}\right)\left(\frac{1}{1+pd\frac{L_1}{L}\frac{1}{L^{1/2}}}\right) \\
&= \quad -pda_1^{3/2}a_2^{1/2}.
\end{aligned} \tag{4.33}$$

Hence,

$$\gamma(-\infty) = \gamma_1(-\infty) - \gamma_2(-\infty) = pd(a_1a_2)^{1/2}. \tag{4.34}$$

Therefore, using equations (4.29), (4.30) and (4.34) we have

$$\theta(-\infty)\gamma(-\infty)\Delta\Lambda(-\infty) = \rho_1 dp(1-p)(a_1a_2)^{1/2}. \tag{4.35}$$

Case 2: $t > -\infty$

For $T(\infty, K_{PP}^L)$, the weight function takes the form given by equation (3.12). Here

$$\begin{aligned}
&K_{PP}^L(s) \\
&= \left(\frac{L}{L_1L_2}\right)^{1/2}\left\{\tilde{S}^L(s-)\frac{Y(s)}{Y(s)+1}\right\}\left(\frac{Y_1(s)Y_2(s)}{Y(s)}\right) \\
&= \left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\tilde{S}^L(s-)\frac{Y(s)}{Y(s)+1}\right\}\left(\frac{Y_1(s)}{L_1}\right)\left(\frac{Y_2(s)}{L_2}\right)\left(\frac{L}{Y(s)}\right).
\end{aligned} \tag{4.36}$$

Hence from equation (4.36), assumption 3.1, and lemma 3.1, we have,

$$\begin{aligned}
&\theta_{PP}(s) \\
&= \lim_{L\to\infty}\left(\frac{L}{L_1L_2}\right)^{1/2} K_{PP}^L(s) \\
&= \lim_{L\to\infty}\left\{\tilde{S}^L(s-)\frac{Y(s)}{Y(s)+1}\right\}\left(\frac{Y_1(s)}{L_1}\right)\left(\frac{Y_2(s)}{L_2}\right)\left(\frac{L}{Y(s)}\right) \\
&= S(s-)\frac{\pi_1(s)\pi_2(s)}{(a_1\pi_1(s)+a_2\pi_2(s))}.
\end{aligned} \tag{4.37}$$

Similarly for $T(\infty, K_L^L)$ we have

$$\theta_L(s) = \frac{\pi_1(s)\pi_2(s)}{(a_1\pi_1(s) + a_2\pi_2(s))}. \tag{4.38}$$

Since $f(t)$ is absolutely continuous and $f_1^L(t) = f(t + c\alpha_1\Delta^L)$, we have

$$\begin{aligned}
\lambda_{1(cont)}^L(t) &= \frac{f(t + c\alpha_1\Delta^L)}{F(t + c\alpha_1\Delta^L)} = \lambda(t + c\alpha_1\Delta^L) \\
\Rightarrow \quad \frac{d\Lambda_1^L(t)}{d\Lambda(t)} &= \frac{\lambda_1^L(t)}{\lambda(t)} = \frac{\lambda(t + c\alpha_1\Delta^L)}{\lambda(t)}.
\end{aligned} \tag{4.39}$$

From the Taylor's expansion in equation (4.39), around $\Delta^L = 0$, we see

$$\begin{aligned}
\frac{\lambda(t + c\alpha_1\Delta^L)}{\lambda(t)} &= \frac{\lambda(t) + c\alpha_1\Delta^L\lambda'(t) + \Delta^L o(1)}{\lambda(t)} \\
\Rightarrow \quad \frac{d\Lambda_1^L(t)}{d\Lambda(t)} &\approx \left\{1 + c\alpha_1\Delta^L\frac{\lambda'(t)}{\lambda(t)} + \frac{\Delta^L o(1)}{\lambda(t)}\right\}.
\end{aligned} \tag{4.40}$$

Using assumption 3.1, equations (4.1) and (4.40),

$$\begin{aligned}
\gamma_1(t) &= \lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\frac{d\Lambda_1^L(t)}{d\Lambda(t)} - 1\right\} \\
&= \lim_{L\to\infty}\left\{\left(\frac{L_1}{L}\right)^{1/2}(L_2)^{1/2}c\alpha_1\left(\frac{1}{L}\right)^{1/2}\frac{\lambda'(t)}{\lambda(t)}\right\} \\
&\quad + \lim_{L\to\infty}\left\{\left(\frac{L_1}{L}\right)^{1/2}(L_2)^{1/2}\left(\frac{1}{L}\right)^{1/2}\frac{o(1)}{\lambda(t)}\right\} \\
&= c\alpha_1(a_1a_2)^{1/2}\left(\frac{\lambda'(t)}{\lambda(t)}\right).
\end{aligned} \tag{4.41}$$

It can be shown that on each closed subinterval of $\{t : F(t-) < 1$, the convergence is uniform. Following the arguments in equation (4.41), we see that

$$\gamma_2(t) = \lim_{L\to\infty}\left(\frac{L_1L_2}{L}\right)^{1/2}\left\{\frac{d\Lambda_2(t)}{d\Lambda(t)} - 1\right\} = -c\alpha_2(a_1a_2)^{1/2}\left(\frac{\lambda'(t)}{\lambda(t)}\right). \tag{4.42}$$

Using equations (4.41) and (4.42), we see that

$$\gamma(t) = \gamma_1(t) - \gamma_2(t) = c(a_1 a_2)^{1/2}\Big(\frac{\lambda'(t)}{\lambda(t)}\Big). \tag{4.43}$$

Since we are assuming absolutely continuous distributions, under a sequence of contiguous alternatives, based on equation (4.1), condition (4.5) of theorem 4.1 is satisfied.

The existence of γ_i is established by equations (4.32), (4.33), (4.41), and (4.42). Further,

$$\begin{aligned}\int_{[-\infty,t]} |\gamma_1| d\Lambda &= |\gamma_1(-\infty)|\Delta\Lambda(-\infty) + \int_{(-\infty,t]} |\gamma_1| d\Lambda \\ &= pda_1^{1/2}a_2^{3/2}(1-p) + \int_{(-\infty,t]} c\alpha_1(a_1a_2)^{1/2}\Big|\frac{\lambda'(s)}{\lambda(s)}\Big| d\Lambda(s). \end{aligned} \tag{4.44}$$

The finiteness of equation (4.44), for $t \in \mathcal{I}$, is clear under assumption 4.1. Condition (4.7) is now satisfied.

Condition (4.8) has been established in equations (4.30), (4.37) and (4.38).

For conditions (4.13) and (4.17), note that for $s = -\infty$,

$$\frac{d\Lambda_1^L}{d\Lambda_2^L} = \frac{(1-p_1^L)}{(1-p_2^L)}. \tag{4.45}$$

And for $s > -\infty$,

$$\frac{d\Lambda_1^L}{d\Lambda_2^L} = \frac{\lambda_1^L}{\lambda_2^L} = \frac{\lambda(t + c\alpha_1\Delta^L)}{\lambda(t - c\alpha_2\Delta^L)}. \tag{4.46}$$

For equations (4.45) and (4.46), using equation (4.1) and assumption 4.2, as $L \to \infty$

$$\frac{d\Lambda_1^L}{d\Lambda_2^L} \to 1 < \infty. \tag{4.47}$$

By equation (4.47) conditions (4.13) and (4.17) are satisfied.

Condition (2b) on page 39 is the same as condition (2a) on page 24 and hence has already been established.

For for some of the remaining proofs the inequalities

$$\left(\frac{L}{L_1L_2}\right)\left(\frac{Y_1Y_2}{Y}\right)\left(\frac{1}{Y_1}\right) \leq \left(\frac{Y_1}{L_1}\frac{Y_2}{L_2}\frac{L}{Y}\right) \leq \left(\frac{L}{L_2}\right)\left(\frac{Y_1}{L_1}\right) \tag{4.48}$$

and

$$\left(\frac{L}{L_1L_2}\right)\left(\frac{Y_1Y_2^2}{Y^2}\right) \leq \left(\frac{L}{L_2}\right)\left(\frac{Y_1}{L_1}\right) \tag{4.49}$$

will be used.

Conditions (2c) and (3b) will be shown for Peto & Peto (1972) scores. Arguments involving logrank scores are simpler than those involving Peto & Peto (1972) scores and hence follow immediately. Note

$$\begin{aligned}
&\int_{[t,u]} \frac{\{K_{PP}^L\}^2}{Y_1} d\Lambda_1^L(s) \\
&= \frac{\{K_{PP}^L(-\infty)\}^2}{Y_1(-\infty)} \Delta\Lambda_1^L(-\infty) I_{\{t=-\infty\}} \\
&\quad + \int_{(t,u]} \left(\frac{L}{L_1L_2}\right)\left\{\tilde{S}(-)\frac{Y}{Y+1}\right\}^2 \left(\frac{Y_1Y_2}{Y}\right)^2 \frac{1}{Y_1}\left(\frac{d\Lambda_1^L(s)}{d\Lambda(s)}\right) d\Lambda(s) \\
&= \frac{\rho_1^2}{L_1}(1-p_1^L) I_{\{t=-\infty\}} \\
&\quad + \int_{(t,u]} \left(\frac{L}{L_1L_2}\right)\left\{\tilde{S}(-)\frac{Y}{Y+1}\right\}^2 \left(\frac{Y_1Y_2}{Y}\right)^2 \frac{1}{Y_1}\left(\frac{\lambda(s+c\alpha_1\Delta^L)}{\lambda(s)}\right) d\Lambda(s).
\end{aligned} \tag{4.50}$$

If $t \in (L', u)$ then by equation 4.49 and assumption 4.2

$$\begin{aligned}
&\left| \int_{[t,u]} \frac{\{K_{PP}^L\}^2}{Y_1} d\Lambda_1^L(s) \right| \\
&\leq \quad Q_2 \frac{L}{L_2} \int_{(t,u]} \left(\frac{Y_1}{L_1}\right) d\Lambda(s) \\
&\xrightarrow{L\to\infty} \quad \frac{1}{a_2} \int_{(t,u]} \pi_1(s) d\Lambda(s), \qquad (4.51)
\end{aligned}$$

where the latter follows from Lemma 7.2.2 of Fleming & Harrington (1991).

Condition (2c) is now satisfied. From the fact that

$$\frac{(K_{PP}^L)^2}{Y_1} = \left(\frac{L}{L_1 L_2}\right) \tilde{S}(-) \frac{Y_1 Y_2^2}{(Y+1)^2} = 0$$

almost certainly on $[u, \infty)$ condition (3b) is satisfied.

Recall that ρ_1 is a misspecified value of true ρ. Arguments for condition (2d) will involve both ρ and ρ_1. For condition (2d) note

$$\begin{aligned}
&\int_{\mathcal{I}} |\theta_{PP}\gamma_1| d\Lambda \\
&= \quad \Big|\theta_{PP}(-\infty)\gamma_1(-\infty)\Big| \Delta\Lambda(-\infty) + \int_{(-\infty,\infty)} \Big|\theta_{PP}(t)\gamma_1(t)\Big| d\Lambda(t). \qquad (4.52)
\end{aligned}$$

Using equations (4.29), (4.30) and (4.32) the first term in equation (4.52) is

$$\left(\rho_1 p d a_1^{1/2} a_2^{3/2}\right)(1-p) < \infty.$$

Using equation (4.37) and (4.41) the second term in equation (4.52) is

$$c\alpha_1 (a_1 a_2)^{1/2} \int_{(-\infty,\infty)} S(t-) \frac{\pi_1(t)\pi_2(t)}{(a_1\pi_1(t) + a_2\pi_2(t))} \left|\frac{\lambda'(t)}{\lambda(t)}\right| d\Lambda. \qquad (4.53)$$

Under assumption 4.1 on page 41 and the arguments in (3.16), the finiteness of equation (4.53) is clear. Thus condition (2d) is satisfied.

Assuming that at least one subject in each group responds it suffices to verify conditions (2e) and (3c) only for $t > -\infty$. Note that

$$\int_{[t,u]} |K^L_{PP}| \left|\frac{d\Lambda^L_1}{d\Lambda} - 1\right| d\Lambda$$

$$= \int_{[t,u]} \left(\frac{L_1 L_2}{L}\right)^{1/2} \left\{\tilde{S}(-)\frac{Y}{Y+1}\right\} \left(\frac{Y_1}{L_1}\frac{Y_2}{L_2}\frac{L}{Y}\right) \left|\frac{\lambda(s + c\alpha_1 \Delta^L)}{\lambda(s)} - 1\right| d\Lambda$$

$$= \int_{[t,u]} \left(\frac{L_1 L_2}{L}\right)^{1/2} \left\{\tilde{S}(s-)\frac{Y}{Y+1}\right\} \left(\frac{Y_1}{L_1}\frac{Y_2}{L_2}\frac{L}{Y}\right) c\alpha_1 \Delta^L \left|\frac{\lambda'(\xi)}{\lambda(\xi)}\frac{\lambda(\xi)}{\lambda(s)}\right| d\Lambda.$$

Using assumptions 4.1 and 4.2, this is bounded above by

$$QQ_2 \int_{[t,u]} \left(\frac{L_1}{L}\right)^{1/2} \left(\frac{L_2}{L}\right)^{1/2} \left(\frac{Y_1}{L_1}\frac{Y_2}{L_2}\frac{L}{Y}\right) c\alpha_1 d\Lambda,$$

which, by equation 4.48 is, in turn bounded above by

$$QQ_2 \int_{[t,u]} \left(\frac{L_1}{L}\right)^{1/2} \left(\frac{L_2}{L}\right)^{1/2} \left(\frac{L}{L_2}\right) \left(\frac{Y_1}{L_1}\right) c\alpha_1 d\Lambda$$

$$\xrightarrow{L\to\infty} \quad QQ_2 c\alpha_1 \left(\frac{a_1}{a_2}\right)^{1/2} \int_{[t,u]} \pi_1 d\Lambda$$

$$\xrightarrow{t\uparrow u} \quad 0 \quad (\text{since } a_i \in (0,1)). \tag{4.54}$$

By virtue of equation (4.54) condition (2e) is satisfied. Again using lemma 7.2.2, on page 261 of Fleming & Harrington (1991),

$$\lim_{L\to\infty} \int_{[u,\infty]} \pi_1 d\Lambda = 0$$

and condition (3c) is satisfied.

Now all the conditions of theorem 4.1 are satisfied. The structure of the general formula of efficacy will be derived in section 4.5.

4.5 Derivation of Efficacy

Our goal in this section is to evaluate Pitman's asymptotic relative efficiency (ARE) when the value of the parameter ρ is misspecified. According to Noether's theorem (see Randles & Wolfe 1991), the ARE between two statistics, V and W, denoted by $ARE(V, W)$, is defined in terms of the respective efficacies of the statistics V and W. The efficacy of the statistic

$$\frac{T(\infty, K^L)}{\hat{\sigma}(\infty)}$$

is defined as:

$$\begin{aligned} e(\theta, \infty) &= \left[\frac{\mu(\infty)}{\sigma(\infty)}\right]^2 \\ &= \frac{\left(\int_{[-\infty,\infty]} \theta(s)\gamma(s)d\Lambda(s)\right)^2}{\int_{[-\infty,\infty]} \frac{(a_1\pi_1+a_2\pi_2)}{\pi_1\pi_2}\theta^2(s)\Big(1-\Delta\Lambda(s)\Big)d\Lambda(s)}, \end{aligned} \tag{4.55}$$

where $\mu(\infty)$ and $\sigma(\infty)$ are defined in equations (4.10) and (4.11), respectively. Using the definition of efficacy in (4.55), specific formulæ for efficacy for $T(\infty, K^L_{PP}, \rho_1)$ and $T(\infty, K^L_L, \rho_1)$ will be derived. Note that here we are interested in efficacy when ρ_1 is a misspecified value of ρ.

4.5.1 Efficacy Formulæ

From Gill (1980) we know that the optimum choice of the weight function $K(t)$ is such that

$$\theta(t) = \left(\frac{\lambda'(t)}{\lambda(t)}\right)\left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\right). \tag{4.56}$$

In this section we shall give the formula for efficacy for the optimal choice of the weight function, based on (4.55). However, we will assume that ρ_1 is a misspecified value of ρ.

Efficacy for Peto & Peto (1972) version of combined test

From (4.10) and (4.11), for $T(\infty, K^L_{PP}, \rho_1)$,

$$\mu_{PP}(\infty) = \int_{[-\infty,\infty]} \theta_{PP}(t)\gamma(t)d\Lambda(t)$$

$$= c(a_1a_2)^{1/2} \int_{(-\infty,\infty]} S(t)\left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\right)\frac{\lambda'(t)}{\lambda(t)}d\Lambda(t) + \rho_1 dp(1-p)(a_1a_2)^{1/2}$$

$$= c(a_1a_2)^{1/2}\left[\int_{(-\infty,\infty]} S(t)\left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\right)\lambda'(t)dt + \rho\rho_1 p(1-p)\right] \tag{4.57}$$

and

$$\sigma^2_{PP}(\infty) = \int_{[-\infty,\infty]} \frac{a_1\pi_1(t)+a_2\pi_2(t)}{\pi_1(t)\pi_2(t)}\theta^2(t)(1-\Delta\Lambda(t))d\Lambda(t)$$

$$= \left[\int_{(-\infty,\infty]} S^2(t)\left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\right)\Big(1-\Delta\Lambda(t)\Big)d\Lambda(t)\right.$$

$$\left. + \rho_1^2 p(1-p)\right]$$

$$= \left[\int_{(-\infty,\infty]} S^2(t)\left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\right)\lambda(t)dt + \rho_1^2 p(1-p)\right]. \tag{4.58}$$

If the underlying distribution is logistic then

$$S(t) = \frac{1}{1+e^t},$$

$$\lambda(t) = \frac{e^t}{1+e^t}$$

and

$$\lambda'(t) = \frac{e^t}{(1+e^t)^2}.$$

Hence from (4.57) and (4.58)

$$\begin{aligned}
\mu_{PP}(\infty) &= c(a_1a_2)^{1/2}\Big[\int_{(-\infty,\infty]} \frac{1}{(1+e^t)}\Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\Big)\frac{e^t}{(1+e^t)^2}dt \\
&\qquad +\rho\rho_1 p(1-p)\Big] \\
&= c(a_1a_2)^{1/2}\Big[\int_{(-\infty,\infty]} \frac{e^t}{(1+e^t)^3}\Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\Big)dt + \rho\rho_1 p(1-p)\Big] \qquad (4.59)
\end{aligned}$$

and

$$\begin{aligned}
\sigma^2_{PP}(\infty) &= \Big[\int_{(-\infty,\infty]} \frac{1}{(1+e^t)^2}\Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\Big)\frac{e^t}{(1+e^t)}dt \\
&\qquad +\rho_1^2 p(1-p)\Big] \\
&= \Big[\int_{(-\infty,\infty]} \frac{e^t}{(1+e^t)^3}\Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\Big)dt + \rho_1^2 p(1-p)\Big]. \qquad (4.60)
\end{aligned}$$

Using (4.55), (4.59), and (4.60) the efficacy for a misspecification of ρ is

$$\begin{aligned}
&e(\theta_{PP}, \rho, \rho_1, \infty) \\
&= \frac{c^2a_1a_2\Big[\int_{(-\infty,\infty]} \frac{e^t}{(1+e^t)^3}\Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\Big)dt + \rho\rho_1 p(1-p)\Big]^2}{\Big[\int_{(-\infty,\infty]} \frac{e^t}{(1+e^t)^3}\Big(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)}\Big)dt + \rho_1^2 p(1-p)\Big]}. \qquad (4.61)
\end{aligned}$$

Efficacy for logrank version of combined test

Again using (4.10) and (4.11), for $T(\infty, K_L^L, \rho_1)$,

$$\mu_L(\infty) = \int_{[-\infty,\infty]} \theta_L(t)\gamma(t)d\Lambda(t)$$

$$= c(a_1a_2)^{1/2} \int_{(-\infty,\infty]} \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)\frac{\lambda'(t)}{\lambda(t)}d\Lambda(t) + \rho_1 dp(1-p)(a_1a_2)^{1/2}$$

$$= c(a_1a_2)^{1/2}\left[\int_{(-\infty,\infty]} \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)\lambda'(t)dt + \rho\rho_1 p(1-p)\right] \tag{4.62}$$

and

$$\sigma_L^2(\infty) = \left[\int_{(-\infty,\infty]} \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)\Big(1 - \Delta\Lambda(t)\Big)d\Lambda(t)\right.$$

$$\left. + \rho_1^2 p(1-p)\right]$$

$$= \left[\int_{(-\infty,\infty]} \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)\lambda(t)dt + \rho_1^2 p(1-p)\right]. \tag{4.63}$$

If the underlying distribution is extreme minimum value, then

$$S(t) = e^{-e^t},$$

$$\lambda(t) = e^t$$

and

$$\lambda'(t) = e^t.$$

Hence, from (4.62) and (4.63)

$$\mu_L(\infty) = c(a_1a_2)^{1/2}\left[\int_{(-\infty,\infty]} e^t\left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)}\right)dt + \rho\rho_1 p(1-p)\right] \tag{4.64}$$

and

$$\sigma_L^2(\infty) = \left[\int\limits_{(-\infty,\infty]} e^t \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t) + a_2\pi_2(t)} \right) dt + \rho_1^2 p(1-p) \right]. \tag{4.65}$$

Using (4.55), (4.64), and (4.65) the efficacy for a misspecification of ρ is

$$e(\theta_L, \rho, \rho_1, \infty)$$

$$= \frac{c^2 a_1 a_2 \left[\int\limits_{(-\infty,\infty]} e^t \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)} \right) dt + \rho\rho_1 p(1-p) \right]^2}{\left[\int\limits_{(-\infty,\infty]} e^t \left(\frac{\pi_1(t)\pi_2(t)}{a_1\pi_1(t)+a_2\pi_2(t)} \right) dt + \rho_1^2 p(1-p) \right]}. \tag{4.66}$$

Note:

1. The efficacies given above are for the cases where the optimal weight function was used for each underlying density, yet, $\rho_1 \neq \rho$. This will enable us to evaluate the loss in efficiency when ρ is misspecified.

2. The Asymptotic Relative Efficiency (ARE) of one statistic T with respect to another W is defined as the ratio of their respective efficacies. In other words

$$ARE(T, W) = \frac{e(T, \infty)}{e(W, \infty)}.$$

   $ARE(T, W) = 1.2$ implies that in order to achieve the same power W requires a sample size which is 20% larger than that required by T.

3. The constants c^2, a_1, and a_2 in the formulæ (4.61) and (4.66) do not play any role in the computation of the corresponding AREs.

4. $\pi_1(s)$ and $\pi_2(s)$ are defined in chapter 3.

4.6 Computed AREs and Efficacies

In this section efficacies for various settings of the parameters are computed. Computations are performed using the formulæ given in equations (4.61) for Peto & Peto's version of our test statistic and in equation (4.66) for the logrank version of our test statistic.

Parameter Settings

1. $\rho = (0.05, 0.2, 1, 3, 10)$.

   Note that ρ is the true value of ρ, and $\rho_1 = (0.05, 0.2, 1, 3, 10)$ are misspecified values of ρ.

2. Densities considered are :

   extreme minimum value and logistic.

3. Censoring parameter :

   $\alpha_1 =$ (0, 2, 4), for group 1.

   $\alpha_2 =$ (0, 2, 4), for group 2.

   Note that $\alpha_i = 0$, $\alpha_i = 2$ and $\alpha_i = 4$ imply no censoring, light censoring and heavy censoring respectively. The censoring distribution used to compute efficacies was extreme minimum value

   $$L(x) = 1 - e^{(x - log(1/\alpha) - e^{(x - log(1/\alpha))})}; \quad -\infty < x < \infty, \quad \alpha > 0.$$

4. Proportion of responders :

   $p = (0.2, 0.5, 0.8)$. Hence we are looking at low to high percentage of response rates.

Integration in the formulæ were performed numerically using the Midpoint-Simpson rule as cited in Thisted (1988). The algorithm for the Midpoint-Simpson rule, given

on page 275 in Thisted (1988), was implemented in our computations. The prime reason for selecting Simpson's rule was due to the relative simplicity of our integrals. For more complicated integrals, one could use other numerical integration techniques, namely the quadrature fomulæ. Amongst various Simpson's rules, the midpoint rule enables us to evaluate integrals with singularities at the end points of integrals. This is especially important since limits of integration in formulæ (4.61) and (4.66) are $(-\infty, \infty]$. Efficacy plots revealed that efficacies approached an asymptote soon beyond $log(t) = log(4)$. Hence all integrals were evaluated over $(-\infty, log(4)]$.

Tables 4.1, 4.3, and 4.5 give computed efficacies when the underlying density is logistic, with weights (for the linear rank test) also generated from the logistic density. Tables 4.7, 4.9, and 4.11, on the other hand, give computed efficacies when the underlying density is extreme minimum value, with weights generated from the extreme minimum value density. In other words, these tables give efficacies for the locally most powerful test when the constant parameter ρ is misspecified. Tables 4.2, 4.4, 4.6, 4.8, 4.10, and 4.12 give the corresponding Pitman's ARE values.

Description of Tables 4.1 - 4.12

Each table is split in three boxes stacked vertically, for $p = 0.2$, $p = 0.5$, and $p = 0.8$. The second column gives the true values of ρ. The top row shows values that ρ could take if it were misspecified. The entries in the body of the tables are the computed efficacies or AREs, as may be the case. Note that in all these cases we are looking at efficacies when censoring in both the groups is equal. Gill (1980) pointed out that this is the case when efficacy is maximum.

Each entry in tables 4.2, 4.4, 4.6, 4.8, 4.10, and 4.12 are computed using the formula

$$ARE(\rho_1, \rho) = \frac{eff(\rho_1, \rho)}{eff(\rho, \rho)},$$

using corresponding entries from tables 4.1, 4.3, 4.5, 4.7, 4.9, and 4.11, respectively.

Tables 4.2, 4.4, and 4.6 give the AREs for misspecification of ρ when the underlying density is logistic and the scores are generated from the logistic density, for censoring parameter $\alpha = 0$, $\alpha = 2$, and $\alpha = 4$, respectively.

Tables 4.8, 4.10, and 4.12 give the ARE's for misspecification of ρ when the underlying density is extreme minimum value and the scores are generated from the extreme minimum value density, for censoring parameter $\alpha = 0$, $\alpha = 2$, and $\alpha = 4$ respectively.

Discussion For Misspecification of ρ

Efficacies

Consider tables 4.1, 4.3, 4.5, 4.7, 4.9, and 4.11.

1. The efficacies behave differently for $\rho < 1$ and $\rho > 1$. When $\rho < 1$, for a fixed ρ (say $\rho = 0.05$), the efficacies increase as p goes from 0.2 to 0.8. On the other hand when $\rho > 1$ the efficacies increase in the interval $(0 \leq p \leq 0.5)$ and then decrease in the interval $(0.5 \leq p \leq 1)$. This feature can be observed if one glanced down the each column (fixed ρ_1) of each table for a fixed values of ρ. One explanation for this is when $\rho < 1 \quad (\Rightarrow d < c)$ our test statistic, given in equation (2.19), is dominated by the shift in the survival times (responders). Hence, when p increases, i.e., the proportion of responders increases, the efficacy of $T(\infty, K^L, \rho_1)$ increases almost as closely as Prentice's (1978) T_P statistic. When $\rho > 1 \quad (\Rightarrow d > c)$, it is clear that $T(\infty, K^L, \rho_1)$, given in equation (2.19), is dominated by the binomial component B, which is a test for a difference of two proportions. Hence it is expected that in such an event $T(\infty, K^L, \rho_1)$ will behave like a binomial test. Consequently such a test will have the highest efficacy when $p = 0.5$.

2. For each value of p and α the efficacies when $\rho_1 = \rho$ is highest. These values are the entries along the main diagonal in each table, for fixed p.

3. Scanning across tables 4.1, 4.3, and 4.5 it is evident that as the degree of censoring increases from light ($\alpha = 0$) to heavy ($\alpha = 4$) the efficacies drop. This decline in efficacy as the rate of censoring increases is more pronounced when $\rho < 1$ than when $\rho > 1$.

AREs

Consider tables 4.2, 4.4, 4.6, 4.8, 4.10, and 4.12. These tables show the loss in AREs for a misspecification of ρ.

1. For each fixed censoring rate and proportion of responders, evidently, as ρ_1 moves farther away from the true value of ρ, there is likely to be a loss in Pitman's ARE.

2. The loss in efficiency is more sensitive for $\rho_1 \leq 1$ than that for $\rho_1 \geq 1$.

3. Of importance is the case when $\rho_1 = 1$. This is when the shift for the failure time distribution and that for the log-odds are equal. This is also, as a result, the case when one treats the nonresponders as responders and performs a classical two-sample test. The column for $\rho_1 = 1$ for all the tables for ARE shows the loss in efficiencies when ρ_1 is misspecified.

   Logistic

   For each degree of censoring, the AREs increase as the rate of responders increases form 0.2 to 0.8, when $\rho < 1$. However, when $\rho > 1$ the AREs decrease as the rate of responders increase from $p = 0.2$ to $p = 0.8$. This is possibly because when $\rho > 1$ our test based on T is dominated by the responders. When rate of censoring increases, for $\rho < 1$, the AREs decrease. However, when $\rho > 1$, the ARE actually increases slightly with an increase in the degree in censoring.

Table 4.1. EFFICACIES for $\alpha_1 = 0$ & $\alpha_2 = 0$, $(\theta, \gamma) = (\text{L}, \text{L})$.

Censoring : $\alpha_1 = 0$ & $\alpha_2 = 0$. Score Generating Distribution = Logistic. Underlying Distribution = Logistic.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	0.06	0.06	0.02	0.00	0.00
	$\rho = 0.2$	0.06	0.07	0.04	0.02	0.01
	$\rho = 1$	0.08	0.13	0.22	0.19	0.17
	$\rho = 3$	0.12	0.37	1.33	1.50	1.47
	$\rho = 10$	0.32	2.18	12.54	15.75	16.06
p=0.5	$\rho = 0.05$	0.15	0.14	0.07	0.01	0.00
	$\rho = 0.2$	0.15	0.16	0.10	0.04	0.02
	$\rho = 1$	0.17	0.25	0.40	0.34	0.28
	$\rho = 3$	0.23	0.56	2.03	2.40	2.33
	$\rho = 10$	0.50	2.65	17.59	24.39	25.15
p=0.8	$\rho = 0.05$	0.24	0.24	0.15	0.04	0.01
	$\rho = 0.2$	0.24	0.24	0.18	0.07	0.02
	$\rho = 1$	0.25	0.30	0.40	0.31	0.21
	$\rho = 3$	0.29	0.46	1.30	1.68	1.56
	$\rho = 10$	0.42	1.27	8.48	15.13	16.24

This is expected, since censoring only affects the failure time distribution and not the rate of responders.

Extreme Minimum Value

The above observations in relation to the logistic distribution is exactly the same as that seen for the extreme minimum value distribution.

Table 4.2. AREs for $\alpha_1 = 0$ & $\alpha_2 = 0$, (θ, γ) = (L, L).

Censoring : $\alpha_1 = 0$ & $\alpha_2 = 0$. Score Generating Distribution = Logistic. Underlying Distribution = Logistic.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	1	1.00	0.33	0.00	0.00
	$\rho = 0.2$	0.85	1	0.57	0.28	0.14
	$\rho = 1$	0.36	0.59	1	0.86	0.77
	$\rho = 3$	0.08	0.25	0.89	1	0.98
	$\rho = 10$	0.02	0.13	0.78	0.98	1
p=0.5	$\rho = 0.05$	1	0.93	0.47	0.06	0.00
	$\rho = 0.2$	0.93	1	0.62	0.25	0.12
	$\rho = 1$	0.42	0.62	1	0.85	0.70
	$\rho = 3$	0.09	0.23	0.84	1	0.97
	$\rho = 10$	0.02	0.10	0.70	0.97	1
p=0.8	$\rho = 0.05$	1	1.00	0.62	0.17	0.04
	$\rho = 0.2$	1.00	1	0.75	0.29	0.08
	$\rho = 1$	0.62	0.75	1	0.77	0.52
	$\rho = 3$	0.17	0.27	0.77	1	0.93
	$\rho = 10$	0.02	0.08	0.52	0.93	1

Table 4.3. EFFICACIES for $\alpha_1 = 2$ & $\alpha_2 = 2$, (θ, γ) = (L, L).

Censoring : $\alpha_1 = 2$ & $\alpha_2 = 2$. Score Generating Distribution = Logistic. Underlying Distribution = Logistic.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	0.04	0.04	0.01	0.00	0.00
	$\rho = 0.2$	0.05	0.05	0.03	0.01	0.01
	$\rho = 1$	0.06	0.12	0.20	0.19	0.17
	$\rho = 3$	0.10	0.39	1.35	1.48	1.46
	$\rho = 10$	0.35	2.61	13.22	15.81	16.05
p=0.5	$\rho = 0.05$	0.11	0.11	0.04	0.01	0.00
	$\rho = 0.2$	0.12	0.12	0.07	0.03	0.01
	$\rho = 1$	0.14	0.21	0.36	0.31	0.27
	$\rho = 3$	0.20	0.56	2.05	2.36	2.31
	$\rho = 10$	0.50	3.08	18.87	24.53	25.11
p=0.8	$\rho = 0.05$	0.18	0.18	0.10	0.03	0.00
	$\rho = 0.2$	0.18	0.18	0.13	0.05	0.02
	$\rho = 1$	0.19	0.24	0.34	0.27	0.20
	$\rho = 3$	0.23	0.41	1.28	1.62	1.53
	$\rho = 10$	0.37	1.34	9.35	15.32	16.18

Table 4.4. AREs for $\alpha_1 = 2$ & $\alpha_2 = 2$, $(\theta, \gamma) =$ (L, L).

Censoring : $\alpha_1 = 2$ & $\alpha_2 = 2$. Score Generating Distribution = Logistic. Underlying Distribution = Logistic.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	1	1.00	0.25	0.00	0.00
	$\rho = 0.2$	1.00	1	0.60	0.20	0.20
	$\rho = 1$	0.30	0.60	1	0.95	0.85
	$\rho = 3$	0.07	0.26	0.93	1	0.99
	$\rho = 10$	0.02	0.16	0.82	0.98	1
p=0.5	$\rho = 0.05$	1	1.00	0.36	0.09	0.00
	$\rho = 0.2$	1.00	1	0.58	0.25	0.08
	$\rho = 1$	0.39	0.58	1	0.86	0.75
	$\rho = 3$	0.08	0.24	0.87	1	0.98
	$\rho = 10$	0.02	0.12	0.75	0.98	1
p=0.8	$\rho = 0.05$	1	1.00	0.55	0.17	0.00
	$\rho = 0.2$	1.00	1	0.72	0.28	0.11
	$\rho = 1$	0.56	0.70	1	0.79	0.59
	$\rho = 3$	0.14	0.25	0.79	1	0.94
	$\rho = 10$	0.02	0.08	0.58	0.95	1

Table 4.5. EFFICACIES for $\alpha_1 = 4$ & $\alpha_2 = 4$, (θ, γ) = (L, L).

Censoring : $\alpha_1 = 4$ & $\alpha_2 = 4$. Score Generating Distribution = Logistic. Underlying Distribution = Logistic.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	0.04	0.03	0.01	0.00	0.00
	$\rho = 0.2$	0.04	0.04	0.02	0.01	0.01
	$\rho = 1$	0.05	0.11	0.20	0.18	0.17
	$\rho = 3$	0.10	0.41	1.36	1.48	1.47
	$\rho = 10$	0.37	3.00	13.66	15.85	16.07
p=0.5	$\rho = 0.05$	0.09	0.09	0.03	0.01	0.00
	$\rho = 0.2$	0.10	0.10	0.06	0.02	0.01
	$\rho = 1$	0.12	0.20	0.34	0.30	0.27
	$\rho = 3$	0.18	0.58	2.08	2.34	2.30
	$\rho = 10$	0.51	3.49	19.74	24.62	25.09
p=0.8	$\rho = 0.05$	0.14	0.14	0.08	0.02	0.00
	$\rho = 0.2$	0.15	0.15	0.10	0.04	0.01
	$\rho = 1$	0.16	0.21	0.30	0.25	0.19
	$\rho = 3$	0.19	0.38	1.28	1.58	1.51
	$\rho = 10$	0.35	1.43	10.02	15.43	16.14

Table 4.6. AREs for $\alpha_1 = 4$ & $\alpha_2 = 4$, $(\theta, \gamma) = (\mathrm{L}, \mathrm{L})$.

Censoring : $\alpha_1 = 4$ & $\alpha_2 = 4$.
Score Generating Distribution = Logistic.
Underlying Distribution = Logistic.

		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	1	0.75	0.25	0.00	0.00
	$\rho = 0.2$	1.00	1	0.50	0.25	0.25
	$\rho = 1$	0.34	0.55	1	0.90	0.85
	$\rho = 3$	0.08	0.28	0.92	1	0.99
	$\rho = 10$	0.02	0.19	0.85	0.99	1
p=0.4	$\rho = 0.05$	1	1.00	0.33	0.11	0.00
	$\rho = 0.2$	1.00	1	0.60	0.20	0.10
	$\rho = 1$	0.35	0.59	1	0.88	0.79
	$\rho = 3$	0.08	0.25	0.89	1	0.98
	$\rho = 10$	0.02	0.14	0.79	0.98	1
p=0.8	$\rho = 0.05$	1	1.00	0.57	0.14	0.00
	$\rho = 0.2$	1.00	1	0.67	0.27	0.06
	$\rho = 1$	0.53	0.70	1	0.83	0.63
	$\rho = 3$	0.12	0.24	0.81	1	0.96
	$\rho = 10$	0.02	0.09	0.62	0.96	1

Table 4.7. EFFICACIES for $\alpha_1 = 0$ & $\alpha_2 = 0$, (θ, γ) = (E, E).

Censoring : $\alpha_1 = 0$ & $\alpha_2 = 0$. **Score Generating Distribution = EMV.** **Underlying Distribution = EMV.**						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	0.20	0.19	0.12	0.03	0.00
	$\rho = 0.2$	0.20	0.20	0.15	0.05	0.02
	$\rho = 1$	0.21	0.26	0.36	0.28	0.20
	$\rho = 3$	0.25	0.42	1.28	1.64	1.54
	$\rho = 10$	0.39	1.32	9.06	15.26	16.20
p=0.5	$\rho = 0.05$	0.49	0.49	0.34	0.10	0.01
	$\rho = 0.2$	0.50	0.50	0.39	0.15	0.04
	$\rho = 1$	0.52	0.58	0.74	0.56	0.35
	$\rho = 3$	0.57	0.82	2.08	2.74	2.51
	$\rho = 10$	0.77	1.96	12.07	23.30	25.49
p=0.8	$\rho = 0.05$	0.79	0.78	0.67	0.29	0.04
	$\rho = 0.2$	0.79	0.79	0.71	0.35	0.07
	$\rho = 1$	0.80	0.84	0.95	0.72	0.34
	$\rho = 3$	0.83	0.98	1.69	2.23	1.86
	$\rho = 10$	0.95	1.54	6.02	14.02	16.79

Table 4.8. AREs for $\alpha_1 = 0$ & $\alpha_2 = 0$, (θ, γ) = (E, E).

Censoring : $\alpha_1 = 0$ & $\alpha_2 = 0$.
Score Generating Distribution = EMV.
Underlying Distribution = EMV.

		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	1	0.95	0.60	0.15	0.00
	$\rho = 0.2$	1.00	1	0.75	0.25	0.10
	$\rho = 1$	0.58	0.72	1	0.78	0.56
	$\rho = 3$	0.15	0.26	0.78	1	0.93
	$\rho = 10$	0.02	0.08	0.56	0.94	1
p=0.5	$\rho = 0.05$	1	1.00	0.69	0.20	0.02
	$\rho = 0.2$	1.00	1	0.78	0.30	0.08
	$\rho = 1$	0.70	0.78	1	0.76	0.47
	$\rho = 3$	0.21	0.30	0.76	1	0.92
	$\rho = 10$	0.03	0.08	0.47	0.91	1
p=0.8	$\rho = 0.05$	1	0.99	0.85	0.37	0.05
	$\rho = 0.2$	1.00	1	0.90	0.44	0.08
	$\rho = 1$	0.84	0.88	1	0.76	0.36
	$\rho = 3$	0.37	0.44	0.76	1	0.83
	$\rho = 10$	0.05	0.09	0.36	0.83	1

Table 4.9. EFFICACIES for $\alpha_1 = 2$ & $\alpha_2 = 2$, (θ, γ) = (E, E).

Censoring : $\alpha_1 = 2$ & $\alpha_2 = 2$. Score Generating Distribution = EMV. Underlying Distribution = EMV.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	0.10	0.10	0.04	0.01	0.00
	$\rho = 0.2$	0.10	0.11	0.07	0.02	0.01
	$\rho = 1$	0.12	0.16	0.26	0.32	0.18
	$\rho = 3$	0.15	0.36	1.29	1.54	1.49
	$\rho = 10$	0.32	1.66	11.12	15.59	16.10
p=0.5	$\rho = 0.05$	0.25	0.25	0.14	0.03	0.01
	$\rho = 0.2$	0.25	0.26	0.18	0.06	0.02
	$\rho = 1$	0.27	0.35	0.50	0.40	0.30
	$\rho = 3$	0.33	0.62	2.00	2.50	2.38
	$\rho = 10$	0.56	2.16	15.13	24.03	25.25
p=0.8	$\rho = 0.05$	0.40	0.40	0.30	0.10	0.01
	$\rho = 0.2$	0.40	0.41	0.33	0.13	0.03
	$\rho = 1$	0.42	0.46	0.56	0.42	0.24
	$\rho = 3$	0.45	0.61	1.38	1.84	1.65
	$\rho = 10$	0.58	1.28	7.14	14.70	16.40

Table 4.10. AREs for $\alpha_1 = 2$ & $\alpha_2 = 2$, $(\theta, \gamma) = $ (E, E).

Censoring : $\alpha_1 = 2$ & $\alpha_2 = 2$. Score Generating Distribution = EMV. Underlying Distribution = EMV.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	1	1.00	0.40	0.10	0.00
	$\rho = 0.2$	0.91	1	0.64	0.18	0.09
	$\rho = 1$	0.46	0.61	1	0.85	0.69
	$\rho = 3$	0.10	0.23	0.84	1	0.97
	$\rho = 10$	0.02	0.10	0.69	0.97	1
p=0.5	$\rho = 0.05$	1	1.00	0.56	0.12	0.04
	$\rho = 0.2$	0.96	1	0.69	0.23	0.08
	$\rho = 1$	0.54	0.70	1	0.80	0.60
	$\rho = 3$	0.13	0.25	0.80	1	0.95
	$\rho = 10$	0.02	0.08	0.60	0.95	1
p=0.8	$\rho = 0.05$	1	1.00	0.75	0.25	0.02
	$\rho = 0.2$	0.97	1	0.80	0.31	0.07
	$\rho = 1$	0.75	0.82	1	0.75	0.43
	$\rho = 3$	0.24	0.33	0.75	1	0.90
	$\rho = 10$	0.03	0.08	0.43	0.90	1

Table 4.11. EFFICACIES for $\alpha_1 = 4$ & $\alpha_2 = 4$, (θ, γ) = (E, E).

Censoring : $\alpha_1 = 4$ & $\alpha_2 = 4$.
Score Generating Distribution = EMV.
Underlying Distribution = EMV.

		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	0.07	0.06	0.02	0.01	0.00
	$\rho = 0.2$	0.07	0.07	0.04	0.02	0.01
	$\rho = 1$	0.08	0.13	0.23	0.20	0.17
	$\rho = 3$	0.12	0.36	1.32	1.51	1.47
	$\rho = 10$	0.32	2.05	12.26	15.72	16.07
p=0.5	$\rho = 0.05$	0.17	0.16	0.08	0.02	0.00
	$\rho = 0.2$	0.17	0.18	0.11	0.04	0.02
	$\rho = 1$	0.19	0.27	0.42	0.35	0.28
	$\rho = 3$	0.25	0.57	2.02	2.42	2.34
	$\rho = 10$	0.51	2.52	17.07	24.32	25.17
p=0.8	$\rho = 0.05$	0.27	0.26	0.18	0.05	0.01
	$\rho = 0.2$	0.27	0.27	0.21	0.08	0.02
	$\rho = 1$	0.28	0.33	0.43	0.33)	0.21
	$\rho = 3$	0.32	0.48	1.31	1.71	1.58
	$\rho = 10$	0.45	1.26	8.17	15.04	16.27

Table 4.12. AREs for $\alpha_1 = 4$ & $\alpha_2 = 4$, (θ, γ) = (E, E).

Censoring : $\alpha_1 = 4$ & $\alpha_2 = 4$. Score Generating Distribution = EMV. Underlying Distribution = EMV.						
		$\rho_1 = 0.05$	$\rho_1 = 0.2$	$\rho_1 = 1$	$\rho_1 = 3$	$\rho_1 = 10$
p=0.2	$\rho = 0.05$	1	0.86	0.28	0.14	0.00
	$\rho = 0.2$	1.00	1	0.57	0.28	0.14
	$\rho = 1$	0.34	0.57	1	0.87	0.74
	$\rho = 3$	0.08	0.24	0.87	1	0.97
	$\rho = 10$	0.02	0.13	0.76	0.98	1
p=0.4	$\rho = 0.05$	1	0.94	0.47	0.12	0.00
	$\rho = 0.2$	0.94	1	0.61	0.22	0.11
	$\rho = 1$	0.45	0.64	1	0.83	0.67
	$\rho = 3$	0.10	0.23	0.83	1	0.97
	$\rho = 10$	0.02	0.10	0.68	0.97	1
p=0.8	$\rho = 0.05$	1	0.96	0.67	0.18	0.04
	$\rho = 0.2$	1.00	1	0.78	0.30	0.07
	$\rho = 1$	0.65	0.77	1	0.77	0.49
	$\rho = 3$	0.19	0.28	0.77	1	0.92
	$\rho = 10$	0.03	0.07	0.50	0.92	1

Discussion For Misspecification of Underlying Distribution

In order to evaluate the loss in ARE when the underlying distribution was misspecified we looked at the efficacies when $\rho_1 = \rho$, and when the censoring in each of the two groups was equal, i.e., $\alpha_1 = \alpha_2$. This way we will be removing a loss in efficiency due to a misspecification of ρ or that due to unequal censoring. All the loss, if any, will be purely due to a misspecification of density. Here it should be noted that by "misspecification of density" we mean that given an underlying distribution of the failure times, one uses a different density to generate the scores. For this purpose we looked at efficacies when the underlying density was logistic and extreme minimum value. Scores were also generated from logistic and extreme minimum value densities. Since the loss in efficiency for misspecification of densities was very minimal (most of the AREs were around 90%), we chose not to tabulate them here.

The fact that there is minimal loss in efficiency when the scores were generated from a different density (different form the underlying density) is not surprising. Here is one instance where the distribution-free nature of our statistic comes into play.

CHAPTER 5
MONTE CARLO STUDIES

5.1 Introduction

The results of Chapters 3 and 4 enable us to evaluate the performance of the linear rank tests, $T(\infty, K, \rho)$, derived for the situation described in section (2.1), involving responders and nonresponders. It has been seen through Tables (4.2), (4.4), and (4.6) (when the underlying distribution is logistic) and (4.8), (4.10), and (4.12) (when the underlying distribution is extreme minimum value) that there is loss in Pitman's ARE when the shift parameters c and d are misspecified. In this current chapter Monte Carlo simulation studies are performed in order to evaluate the power of $T(\infty, K, \rho)$ under different settings based on the amount of location shift, degree of censoring, and sample sizes.

It is clear that the test based on $T(\infty, K, \rho)$ requires a priori knowledge of the value of ρ. In clinical trials one could use a ρ established from a previous study. Also, one could specify a desired value of ρ when designing a clinical trial. In either case one can assume ρ to be prespecified. It is however possible that one could encounter a situation where ρ is unknown. In the following sections results are given of Monte Carlo simulations performed for both cases when ρ is known and when ρ is unknown.

5.2 Monte Carlo Power Calculations When ρ is Assumed Known

In this section we show power calculations from a Monte Carlo study when ρ is assumed known. All simulations were done on the Sun Ultra, Enterprise 450 computer

using Ox 2.0 (Doornik 1998). Random number generators in the Ox 2.0 environment were used to generate all random numbers.

5.2.1 Parameter Settings

The parameter settings considered in the Monte Carlo simulations are:

1. Sample sizes : (300, 400).
2. Proportion of responders: 30% (under H_0).
3. Underlying densities : logistic and extreme minimum value (EMV).
4. Censoring rates : (10%, 40%).
5. Censoring distribution: $\log(\text{Uniform}(0, M))$, where M was determined using the equation
$$P(C < T) = q, \tag{5.1}$$
where $q = \%$ censoring. Equation (5.1) for data from a logistic density with location shift parameter δ is given by
$$\frac{\log(Me^{\delta} + 1)}{Me^{\delta}} = q. \tag{5.2}$$
The corresponding equation when data is generated from an extreme minimum value density, with location shift parameter δ, is
$$\frac{1}{Me^{\delta}}\left(1 - e^{-Me^{\delta}}\right) = q. \tag{5.3}$$
6. c : (2.5, 10).
7. d : (2.5, 10).
8. $\Delta = (0,\ 0.035667)$.
9. Number of runs : 3000.

Description of the Simulation Study

For each setting of c, α, and Δ, numbers of responders were generated from a binomial distribution, with $n = 3000$ and p computed using the equations (2.14) and (2.15). For these observations log-failure times were set at -100 and the censoring indicator was set at uncensored (=1). Failure times for each of the 3000 repetitions were generated from the logistic and the extreme minimum value densities. The different location shifts for each group were added to each observation. For each sample, censoring times were generated from a natural logarithm of a uniform random variable with support $(0, M)$, i.e.,

$$L(x) = 1 - \frac{1}{M}e^{x}; -\infty < x < \log(M), M > 0.$$

Values of M were computed from equations (5.2) and (5.3) to give censoring rates of 10% and 40%. After censoring was incorporated, the average % censoring was computed to check the desired level of censoring over the 3000 samples.

Observed α-levels

Monte Carlo simulations were performed to evaluate the observed α-level for equal samples sizes of 300 for 3000 Monte Carlo runs. Power when $\Delta = 0$ is an observed value of the Type I error rate. The observed α-levels of our combined test, given in equation (2.19), are given in tables 5.1 and 5.2, for data generated from the logistic density and the extreme minimum value densities, respectively. At each setting the observed value of the combined test T was computed for each of the 3000 runs. Then the observed α was obtained by counting the number of observed zs that exceeded 1.96 and those that were below -1.96. The final count was then divided by 3000. In these tables observed α-levels are compared to a nominal $\alpha = 0.0500$. The smallest and the largest observed α, in the Tables 5.1 and 5.2, collectively, are 0.0450 and

Table 5.1. Observed α for $f(x) = \mathit{Logistic}$, $\mathit{Reps} = 3000$.

$\rho = d/c$	Censoring (% Group 1, % Group 2)	Peto & Peto < -1.96	Peto & Peto $> +1.96$	Logrank < -1.96	Logrank $> +1.96$
$\rho = 4$	(10%, 10%)	0.0493	0.0490	0.0497	0.0457
	(10%, 40%)	0.0490	0.0453	0.0507	0.0450
	(40%, 10%)	0.0477	0.0487	0.0490	0.0457
	(40%, 40%)	0.0480	0.0490	0.0520	0.0490
$\rho = 0.25$	(10%, 10%)	0.0483	0.0557	0.0477	0.0487
	(10%, 40%)	0.0517	0.0563	0.0497	0.0537
	(40%, 10%)	0.0487	0.0543	0.0483	0.0533
	(40%, 40%)	0.0483	0.0557	0.0510	0.0537

Table 5.2. Observed α for $f(x) = EMV$, $\mathit{Reps} = 3000$.

$\rho = d/c$	Censoring (% Group 1, % Group 2)	Peto & Peto < -1.96	Peto & Peto $> +1.96$	Logrank < -1.96	Logrank $> +1.96$
$\rho = 4$	(10%, 10%)	0.0523	0.0477	0.0527	0.0563
	(10%, 40%)	0.0503	0.0470	0.0560	0.0473
	(40%, 10%)	0.0490	0.0493	0.0543	0.0503
	(40%, 40%)	0.0500	0.0493	0.0553	0.0500
$\rho = 0.25$	(10%, 10%)	0.0563	0.0527	0.0570	0.0570
	(10%, 40%)	0.0530	0.0500	0.0553	0.0520
	(40%, 10%)	0.0520	0.0530	0.0540	0.0510
	(40%, 40%)	0.0540	0.0500	0.0510	0.0483

0.0570, respectively. A 95% confidence interval around 0.045 and 0.0570 is (0.0376, 0.0524) and (0.0487, 0.0653) respectively. Both these confidence intervals contain 0.0500, implying that, with 95% confidence, all observed alpha's shown in tables 5.1 and 5.2 are significantly close to 0.0500. Hence it can be concluded that T, given in equation (2.19), is able to hold a nominal α-level of 0.0500.

<u>Powers under H_Δ</u>

Consider the tables 5.3 - 5.34. These tables give empirical powers when $\Delta = 0.025$. In each table the first column shows the labels of different tests performed. Specifically, "PP(Pooled)" stands for Peto & Peto's (1972) test performed on the data with nonresponders treated as responders with response duration equal to zero.

Similarly "L(Pooled)" is the corresponding logrank test. The tests with "Combined" in parentheses are the combined tests as given in equation (2.19). The last two rows in each table refer to "Separate" tests for the proportions and the failure times. The powers for separate tests were corrected using Bonferroni's inequality. The second column in each table gives the Monte Carlo power in the respective settings. The column labeled "diff" is the difference in power compared to the LMPT in each different case. For instance, if data is generated from the extreme minimum value density, then we expect the logrank version of our combined test to be locally most powerful. Then "diff" is the difference in power compared to the "L(Combined)" test. The column labeled "SE(diff)" is the upper bound of the estimate of the Monte Carlo error. The formula used is

$$\sqrt{\frac{\hat{p_1}(1-\hat{p_1}) + \hat{p_2}(1-\hat{p_2})}{\text{Number of runs}}}.$$

Note that since any two tests are positively correlated the actual standard error will be smaller than those that have been displayed. The final column in each table displays the number of standard deviations that separates the powers of the other tests from the LMPT.

Logistic density

Tables 5.3-5.18 display the Monte Carlo powers for various settings of the parameters when data is generated from a logistic density. It is clear from all these tables that Peto & Peto's (1972) (combined) test has the highest power. Tables 5.3-5.10 show powers when $\rho = 4$. From these tables we see that the powers for the Peto & Peto "pooled" test is not significantly lower than the Peto & Peto "combined" test. The powers of the logrank(pooled) test is also significantly lower than the Peto & Peto (combined) test. However, for $\rho = 4$, powers for the logrank (combined) does not seem to be significantly lower than that of the Peto & Peto (combined) test. Also

to be noted is that for $\rho = 4$ powers do not drop much as the censoring gets heavier. This is expected since in this case the behavior of the combined test T is dominated by the binomial component of T. Hence a change in the censoring pattern may not affect the power drastically. The fact that there is no significant drop in the power between the Pet & Peto (combined) and the Peto & Peto (pooled) is possible owing to the fact that for $\rho = 4$ the test is dominated by the binomial component T_B and hence in order to notice a significant difference in power one needs to look at a larger departure of ρ from 1.

Tables 5.11-5.18 show powers when $\rho = 0.25$. This is the situation when T_P dominates the behavior of T, refer to equation (2.19). Note that for $\rho = 0.25$ decline in power of all other tests, compared to the Peto & Peto (combined), is more pronounced than when $\rho = 4$. The powers for the logrank (combined) and logrank (pooled) seem to get closer to that of the Peto & Peto (combined) test as the degree of censoring is increased. This happens for equal sample sizes of 300. When sample sizes are unequal, though, the Peto & Peto (combined) test is clearly the most powerful in comparison to any other pooled, combined, or separate test. Overall decline in power when censoring get heavier is more pronounced when $\rho = 0.25$ in comparison to that when $\rho = 4$.

Powers in general are higher when $\rho = 0.25$ than when $\rho = 4$.

In conclusion, for data following a logistic distribution the Peto & Peto (combined) test is consistently more powerful in comparison to Peto & Peto (pooled), logrank(combined), logrank (pooled), and separate tests. In some specific settings the logrank (combined) and the Peto & Peto (pooled) may replace the Peto & Peto (combined) test without a significant loss in power, as discussed above.

Extreme Minimum Value Density

Tables 5.19-5.34 give powers from a Monte Carlo simulation with data generated from the extreme minimum value density. Tables 5.19-5.26 give the powers when $\rho = 4$. And tables 5.27-5.34 show powers when $\rho = 0.25$. Tables 5.19-5.22 show powers for equal sample sizes, namely $L_1 = L_2 = 300$, for censoring patterns being (10%, 10%), (10%, 40%), (40%, 10%), and (40%, 40%), in the two groups, when $\rho = 4$. Tables 5.27-5.30 show powers for the same set of pattern of censoring as mentioned above, with equal sample sizes, but now for $\rho = 0.25$. The tables 5.23-5.26 and those labeled as 5.31-5.34 show powers when sample sizes are unequal, namely $L_1 = 300$ and $L_2 = 400$. All powers are computed at $\alpha = 0.05$.

From the above tables, clearly, neither of the separate tests perform well in every setting compared to the combined version of the logrank test. It is also clear that, when $\rho = 4$, Peto & Peto (pooled) and (combined) tests both seem not to lose significant power. Overall powers when one of the samples is of size 400 is higher than those for equal sample sizes of 300. The decline in separation in power of Peto & Peto (combined) test compared to the combined logrank test is more pronounced when the sample sizes are unequal.

When $\rho = 0.25$, the power for the logrank (combined) test is highest when compared to all other comparable tests.

In conclusion, for data following an extreme minimum value distribution, logrank (combined) test is consistently more powerful in comparison to logrank (pooled), Peto & Peto (combined), Peto & Peto (pooled), and separate tests. In some specific settings the Peto & Peto (combined) test may replace the logrank (combined) without a significant loss in power.

Conclusion

Overall, according to the Monte Carlo simulation study, the combined test using a prespecified value of ρ given by equation (3.1) is significantly more powerful than pooled tests or separate tests, barring exceptions mentioed above. Since the significance is with reference to an upper bound of the standard error of the Monte Carlo powers, in reality evidence will be stronger if one were to compute the respective covariances for comparing the powers. Owing to time and resource constraints simulations were performed for 3000 Monte Carlo runs. In order to get a smaller Monte Carlo standard error a larger scale simulation is required. A larger scale simulation is likely to reveal a greater separation in power between tests. When $\rho > 1$ additional simulations, with $\rho > 4$, is likely to show a clear advantage of the "Combined" tests over the "Pooled" tests.

Table 5.3. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.64800	0.00367	0.0123	0.298
PP(Combined)	0.65167	-	-	-
L(Pooled)	0.47167	0.18000	0.0126	14.286
L(Combined)	0.64333	0.00834	0.0123	0.678
Proportions	0.51767	0.13400	0.0126	10.635
Times	0.05200	0.59967	0.0096	62.466

Table 5.4. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.64800	0.00167	0.0123	0.136
PP(Combined)	0.64967	-	-	-
L(Pooled)	0.44900	0.20067	0.0126	15.926
L(Combined)	0.64400	0.00567	0.0123	0.461
Proportions	0.51767	0.13200	0.0126	10.476
Times	0.05433	0.59534	0.0096	62.014

Table 5.5. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.65100	0.00033	0.0123	0.027
PP(Combined)	0.65133	-	-	-
L(Pooled)	0.47767	0.17366	0.0126	13.782
L(Combined)	0.64900	0.00233	0.0123	0.189
Proportions	0.51767	0.13366	0.0126	10.608
Times	0.05633	0.59500	0.0097	61.340

Table 5.6. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.65000	0.00100	0.0123	0.081
PP(Combined)	0.65100	-	-	-
L(Pooled)	0.48067	0.17033	0.0126	13.518
L(Combined)	0.64733	0.00367	0.0123	0.298
Proportions	0.51767	0.13333	0.0126	10.579
Times	0.05300	0.59800	0.0096	62.292

Table 5.7. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 400$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.68267	0.00309	0.0120	0.258
PP(Combined)	0.68567	-	-	-
L(Pooled)	0.50000	0.18576	0.0124	14.981
L(Combined)	0.68000	0.00576	0.0120	0.480
Proportions	0.55667	0.12909	0.0124	10.410
Times	0.06133	0.62442	0.0095	65.729

Table 5.8. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 400$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.68300	0.00233	0.0120	0.194
PP(Combined)	0.68533	-	-	-
L(Pooled)	0.52000	0.16533	0.0124	13.333
L(Combined)	0.68433	0.00100	0.0120	0.083
Proportions	0.55667	0.12866	0.0124	10.376
Times	0.06367	0.62166	0.0095	65.438

Table 5.9. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 400$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.68433	0.00267	0.0120	0.222
PP(Combined)	0.68700	-	-	-
L(Pooled)	0.50833	0.17867	0.0124	14.409
L(Combined)	0.68367	0.00333	0.0120	0.278
Proportions	0.55667	0.13033	0.0124	10.510
Times	0.05500	0.63200	0.0094	67.234

Table 5.10. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 400$, $f(x) =$ *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.68500	0.00033	0.0120	0.0275
PP(Combined)	0.68533	-	-	-
L(Pooled)	0.52500	0.16033	0.0124	12.930
L(Combined)	0.68433	0.00100	0.0120	0.083
Proportions	0.55667	0.12866	0.0124	10.376
Times	0.06267	0.62266	0.0095	65.543

Table 5.11. Power for $\rho = 0.25$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = Logistic$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.18033	0.24634	0.0114	21.372
PP(Combined)	0.42667	-	-	-
L(Pooled)	0.34233	0.08434	0.0132	6.389
L(Combined)	0.36067	0.06600	0.0126	5.238
Proportions	0.07467	0.35200	0.0102	34.510
Times	0.23367	0.19400	0.0119	16.302

Table 5.12. Power for $\rho = 0.25$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = Logistic$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.18000	0.24.367	0.0114	21.374
PP(Combined)	0.42367	-	-	-
L(Pooled)	0.33600	0.08767	0.0132	60642
L(Combined)	0.37267	0.05100	0.0126	4.048
Proportions	0.07467	0.34900	0.0102	34.216
Times	0.24000	0.18367	0.0119	15.434

Table 5.13. Power for $\rho = 0.25$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = Logistic$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.17867	0.24033	0.0114	21.082
PP(Combined)	0.41900	-	-	-
L(Pooled)	0.33800	0.08100	0.0132	6.136
L(Combined)	0.37033	0.04570	0.0126	3.627
Proportions	0.07467	0.34433	0.0102	33.758
Times	0.24533	0.17367	0.0119	14.594

Table 5.14. Power for $\rho = 0.25$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = Logistic$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.17767	0.23733	0.0114	20.818
PP(Combined)	0.41500	-	-	-
L(Pooled)	0.34067	0.07433	0.0132	5.631
L(Combined)	0.37367	0.04133	0.0126	3.280
Proportions	0.07467	0.34033	0.0102	33.366
Times	0.24133	0.17367	0.0119	14.594

Table 5.15. Power for ρ = 0.25, λ_1 = 10%, λ_2 = 10%, L_1 = 300, L_2 = 400, $f(x)$ = *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.20333	0.27867	0.0117	23.818
PP(Combined)	0.48200	-	-	-
L(Pooled)	0.36567	0.11633	0.0127	9.160
L(Combined)	0.39900	0.08300	0.0128	6.484
Proportions	0.07700	0.40500	0.0103	39.320
Times	0.25633	0.22567	0.0121	18.650

Table 5.16. Power for ρ = 0.25, λ_1 = 10%, λ_2 = 40%, L_1 = 300, L_2 = 400, $f(x)$ = *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.20300	0.27100	0.0117	23.162
PP(Combined)	0.47400	-	-	-
L(Pooled)	0.37633	0.09767	0.0127	7.690
L(Combined)	0.40667	0.06733	0.0128	5.260
Proportions	0.07700	0.39700	0.0103	38.544
Times	0.26267	0.21133	0.0121	17.465

Table 5.17. Power for ρ = 0.25, λ_1 = 40%, λ_2 = 10%, L_1 = 300, L_2 = 400, $f(x)$ = *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.20133	0.27434	0.0117	23.448
PP(Combined)	0.47567	-	-	-
L(Pooled)	0.38300	0.09267	0.0127	7.297
L(Combined)	0.42967	0.04600	0.0128	3.594
Proportions	0.07700	0.39867	0.0103	38.706
Times	0.27467	0.20100	0.0121	16.612

Table 5.18. Power for ρ = 0.25, λ_1 = 40%, λ_2 = 40%, L_1 = 300, L_2 = 400, $f(x)$ = *Logistic.*

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.20167	0.26833	0.0117	22.934
PP(Combined)	0.47000	-	-	-
L(Pooled)	0.37033	0.09967	0.0127	7.848
L(Combined)	0.42133	0.04867	0.0128	3.802
Proportions	0.07700	0.39300	0.0103	38.155
Times	0.28167	0.18833	0.0121	15.564

Table 5.19. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.65933	0.00700	0.0122	0.574
PP(Combined)	0.65933	0.00700	0.0122	0.574
L(Pooled)	0.55100	0.11533	0.0125	9.226
L(Combined)	0.66633	-	-	-
Proportions	0.51767	0.14866	0.0125	11.893
Times	0.09000	0.57633	0.0101	57.062

Table 5.20. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.65667	0.00933	0.0122	0.765
PP(Combined)	0.66000	0.00600	0.0122	0.492
L(Pooled)	0.55600	0.11000	0.0125	8.800
L(Combined)	0.66600	-	-	-
Proportions	0.51767	0.14833	0.0125	11.866
Times	0.08700	0.57900	0.0100	57.900

Table 5.21. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.66067	0.00333	0.0122	0.273
PP(Combined)	0.65767	0.00633	0.0122	0.519
L(Pooled)	0.54900	0.11500	0.0125	9.200
L(Combined)	0.66400	-	-	-
Proportions	0.51767	0.14633	0.0125	11.706
Times	0.08500	0.57900	0.0100	57.900

Table 5.22. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.66033	0.00267	0.0122	0.219
PP(Combined)	0.65767	0.00533	0.0122	0.437
L(Pooled)	0.55033	0.11267	0.0125	9.014
L(Combined)	0.66300	-	-	-
Proportions	0.51767	0.14533	0.0125	11.626
Times	0.08167	0.58133	0.0100	58.133

Table 5.23. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.69167	0.01233	0.0118	1.045
PP(Combined)	0.69200	0.01200	0.0118	1.017
L(Pooled)	0.57767	0.12633	0.0123	10.271
L(Combined)	0.70400	-	-	-
Proportions	0.55667	0.14733	0.0123	11.978
Times	0.09433	0.60967	0.0099	61.583

Table 5.24. Power for $\rho = 4$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.69133	0.01067	0.0118	0.904
PP(Combined)	0.69233	0.00967	0.0118	0.819
L(Pooled)	0.58000	0.12200	0.0123	9.919
L(Combined)	0.70200	-	-	-
Proportions	0.55667	0.14533	0.0123	11.815
Times	0.09433	0.60767	0.0099	61.381

Table 5.25. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.69033	0.00770	0.0118	0.652
PP(Combined)	0.69233	0.00867	0.0118	0.735
L(Pooled)	0.58088	0.12012	0.0123	9.766
L(Combined)	0.70100	-	-	-
Proportions	0.55667	0.14433	0.0123	11.734
Times	0.09067	0.61033	0.0099	61.649

Table 5.26. Power for $\rho = 4$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.69100	0.00900	0.0118	0.763
PP(Combined)	0.69233	0.00767	0.0118	0.650
L(Pooled)	0.58400	0.11600	0.0123	9.431
L(Combined)	0.70000	-	-	-
Proportions	0.55667	0.14330	0.0123	11.650
Times	0.09100	0.60900	0.0099	61.515

Table 5.27. Power for $\rho = 0.25$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.22000	0.54967	0.0108	50.895
PP(Combined)	0.66933	0.10034	0.0115	8.725
L(Pooled)	0.66000	0.10967	0.0116	9.454
L(Combined)	0.76967	-	-	-
Proportions	0.07467	0.69500	0.0091	76.374
Times	0.63500	0.13467	0.0117	11.51

Table 5.28. Power for $\rho = 0.25$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.21767	0.52766	0.0109	48.409
PP(Combined)	0.66033	0.08500	0.0117	7.265
L(Pooled)	0.64833	0.09700	0.0118	8.220
L(Combined)	0.74533	-	-	-
Proportions	0.07467	0.67066	0.0093	72.114
Times	0.61533	0.13000	0.0119	10.924

Table 5.29. Power for $\rho = 0.25$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.21800	0.52067	0.0110	47.334
PP(Combined)	0.66133	0.07734	0.0118	6.554
L(Pooled)	0.63267	0.10600	0.0119	8.908
L(Combined)	0.73867	-	-	-
Proportions	0.07467	0.66400	0.0093	71.398
Times	0.60567	0.13300	0.0120	11.083

Table 5.30. Power for $\rho = 0.25$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 300$, $f(x) = EMV$.

	Power	diff	SE(diff)	d/SE(diff)
PP(Pooled)	0.21700	0.50835	0.0111	45.797
PP(Combined)	0.65533	0.07002	0.0119	5.884
L(Pooled)	0.62467	0.10068	0.0120	8.390
L(Combined)	0.72535	-	-	-
Proportions	0.07467	0.65068	0.0094	69.221
Times	0.59300	0.13235	0.0121	10.938

Table 5.31. Power for $\rho = 0.25$, $\lambda_1 = 10\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.24500	0.57167	0.0106	53.931
PP(Combined)	0.72100	0.09567	0.0108	8.858
L(Pooled)	0.71200	0.10467	0.0109	9.603
L(Combined)	0.81667	-	-	-
Proportions	0.07700	0.73967	0.0086	86.008
Times	0.69833	0.11834	0.0110	10.758

Table 5.32. Power for $\rho = 0.25$, $\lambda_1 = 10\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.24400	0.55633	0.0107	51.993
PP(Combined)	0.71267	0.08766	0.0110	7.969
L(Pooled)	0.70100	0.09933	0.0111	8.949
L(Combined)	0.80033	-	-	-
Proportions	0.07700	0.72333	0.0088	82.196
Times	0.68233	0.11800	0.0112	10.536

Table 5.33. Power for $\rho = 0.25$, $\lambda_1 = 40\%$, $\lambda_2 = 10\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.24333	0.54534	0.0108	50.494
PP(Combined)	0.70833	0.08034	0.0112	7.173
L(Pooled)	0.68167	0.10700	0.0113	9.469
L(Combined)	0.78867	-	-	-
Proportions	0.07700	0.71167	0.0090	79.074
Times	0.66167	0.12700	0.0114	11.140

Table 5.34. Power for $\rho = 0.25$, $\lambda_1 = 40\%$, $\lambda_2 = 40\%$, $L_1 = 300$, $L_2 = 400$, $f(x) = EMV$.

	Power	diff	SE(diff)	diff/SE(diff)
PP(Pooled)	0.24167	0.53700	0.0109	49.266
PP(Combined)	0.70233	0.07634	0.0113	6.756
L(Pooled)	0.67333	0.10534	0.0114	9.240
L(Combined)	0.77867	-	-	-
Proportions	0.07700	0.70167	0.0090	77.963
Times	0.65000	0.12867	0.0115	11.189

5.3 Monte Carlo Power Calculations When ρ is Unknown

In this section we will address the situation when ρ is unknown. For demonstrative purposes Monte Carlo powers for data from extreme minimum value density will be shown.

5.3.1 Parameter Settings

The parameter settings considered in the Monte Carlo simulations are:

1. Sample sizes : 500 (each sample).
2. Proportion of responders : 30% (under H_0).
3. Underlying densities : extreme minimum value (EMV).
4. Censoring rates : (40%, 40%).
5. Censoring was incorporated in the data using the exact scheme as discussed in section 5.2.
6. c : (2.5, 10).
7. d : (2.5, 10).
8. For $\rho = 0.25$

   $$\Delta = (0, 0.028768, 0.035667).$$

   For $\rho = 4$

   $$\Delta = (0, 0.025, 0.035).$$

   Note that $\Delta = 0.028768$ and $\Delta = 0.035667$ correspond to 25% and 30% location shift in the failure time distributions between the two samples, respectively.
9. Number of runs : 3000.

Description of the Simulation Study

The simulation study for this section was done along the lines of those when ρ is known. However, in this section ρ was estimated. Estimation of ρ amounts to estimating $c\Delta$ and $d\Delta$. Samples were generated from the exponential density with hazard rate $e^{-c\Delta}$. Under the proportional hazards assumption the location shift $c\Delta$ was estimated by estimating the parameter β through maximizing the likelihood function given by equation (4.6), page 73, Kalbfleisch & Prentice (1980).

For each of the 3000 samples $\widehat{c\Delta}$ was estimated from the proportional hazards model and

$$\widehat{d\Delta} = \log \frac{\hat{p}_2(1-\hat{p}_1)}{\hat{p}_1(1-\hat{p}_2)}.$$

Hence

$$\hat{\rho} = \frac{\widehat{d\Delta}}{\widehat{c\Delta}}.$$

Tables 5.35 and 5.36 show Monte Carlo powers computed for the logrank (pooled), logrank (combined, assuming ρ known), logrank (combined, using $\hat{\rho}$), proportions (separate), and logrank (separate). The nominal α for the "Separate" was fixed at 0.025, using Bonferroni's correction. The observed α levels for logrank (combined, using $\hat{\rho}$) was about 0.0625, which indicated that these tests must be run at $\alpha = 0.04$ instead of at $\alpha = 0.05$. All powers for logrank (combined, using $\hat{\rho}$) shown in tables 5.35 and 5.36 are computed at $\alpha = 0.04$.

From tables 5.35 and 5.36 it is clear that logrank (combined, ρ known) is the most powerful. Moreover, the powers for logrank (combined, using $\hat{\rho}$), albeit lower than those for logrank (combined, ρ known), are higher than those for the logrank (pooled) and the "Separate" tests.

In conclusion, if ρ is unknown then estimating ρ from the data is reasonable. Of course caution must be exercised when estimating ρ in order to maintain high power.

Table 5.35. Empirical powers for $\rho = 4$ (upper one-sided) when ρ is estimated.

Statistics	$\Delta = 0.0000$	$\Delta = 0.0250$	$\Delta = 0.0350$
Logrank (Pooled)	0.05370	0.58533	0.73933
Logrank (Combined, ρ)	0.05470	0.68533	0.84067
Logrank (Combined, $\hat{\rho}$)	0.05270	0.66733	0.81767
Proportions (Separate)	0.02370	0.53867	0.73600
Times (Separate)	0.02970	0.07100	0.09433

Table 5.36. Empirical powers for $\rho = 0.25$ (upper one-sided) when ρ is estimated.

Statistics	$\Delta = 0.0000$	$\Delta = 0.0288$	$\Delta = 0.0357$
Logrank (Pooled)	0.05370	0.48533	0.62433
Logrank (Combined, ρ)	0.05470	0.59800	0.74900
Logrank (Combined, $\hat{\rho}$)	0.05270	0.56400	0.70767
Proportions (Separate)	0.02370	0.07700	0.09367
Times (Separate)	0.02970	0.45300	0.61167

5.4 Estimation of Location-Shift

Owing to the utmost importance in estimating the location-shift parameter in our context, some methods are discussed. In general there are several non-parametric methods for estimating the location shift $c\Delta$. If one prefers not to make many assumptions about the distributions of the true survival times, and if censoring is not present, one of the most widely used robust methods of analysis is the Hodges & Lehmann (1963) approach. Bassiakos et al. (1991) proposed an adaptation of the Hodges-Lehmann shift estimator to take into account censoring. Lai & Ying (1991) establish the large-sample properties of a modified Buckley-James (1979) estimator for the linear regression model. Tsiatis (1990) uses linear rank tests, based on Prentice (1978), to estimate the regression parameters. The equivalence between these two estimators is presented in Ritov (1990).

CHAPTER 6
EXAMPLE

Throughout this dissertation we have so far proposed a test statistic (given by equation (2.19)) that addresses a certain structure of hypothesis (given in equations (2.2) and (2.2)) under a given premise (as given in section 2.1). Subsequently in Chapter 3 we established the asymptotic null distribution of our statistic T. In Chapter 4 we derived the efficacy formula for the statistic T. We also showed some ARE results. Chapter 5 reported Monte Carlo power calculations, which established the strength of the combined test statistic T under various settings. In this chapter we will demonstrate the applicability of our test statistic T with a dataset.

CERAD (Consortium to Establish a Registry for Alzheimer's Disease), funded by the U.S. National Institute of Aging (NIA, grant # AG06790) in 1986, developed a battery of standardized assessments for the evaluation of patients with Alzheimer's Disease (AD). Instruments for the clinical, neuropsychological, and neuropathological assessment of dementia were administered to obtain longitudinal data on subjects enrolled at twenty four university medical centers. Patients and control subjects were evaluated at entry and annually thereafter, to track the natural progression of AD.

Table 6.1 shows a summary of the structure of the CERAD data. A total of 906 AD patients were considered in our analysis. Out of 364 males and 542 females, 181 males and 234 females were institutionalized. Hence the proportions institutionalized were 49.73% for males and 43.17% for females. The median survival times after

instutionalization was 1 year for males and 2.1 years for females. For those institutionalized, the percentage of censoring, with respect to time to death, was 17.58% for males and 23.62% for females.

In order to perform our test based on the statistic T, we need an estimate of $\rho = d/c$. Hence it is sufficient to estimate $c\Delta$ and $d\Delta$. From equation (3.5) it is clear that

$$\widehat{d\Delta} = \log \frac{\hat{p}_1(1-\hat{p}_2)}{\hat{p}_2(1-\hat{p}_1)}.$$

For the CERAD data

$$\widehat{d\Delta} = 0.26379.$$

One could regard the estimation of $c\Delta$ as a problem of estimating the slope parameter, β, in an accelated failure time model. In the analysis of the CERAD data, Buckley & James (1979) iterative procedure for estimating a location shift in censored data was used. The Buckley-James procedure yielded

$$\widehat{c\Delta} = 0.48671.$$

Note that since we would be interested in testing for an increase in median survival times and a decrease in proportions who get institutionalized, for a hypothetical treatment group, we are confronted with a situation which is bidirectional in nature. The alternative hypothesis is given by equation (3.5). Hence the structure of the appropriate test statistic in this case is given by equation (3.6). As per discussion in section 3.2.2 we note that in this case pooled tests in this case must be performed such that those not institutionalized are assumed to be institutionalized at time ∞, uncensored. Table 6.2 gives the observed values of the Z statistic for the different tests. Observe that Peto & Peto's (1972) "Separate" test has a Z_{obs} higher than the Z_{obs} of the logrank test. However, since the observed values of the Z statistic are quite big, we have chosen not to show the respective $p-values$. Neither of the pooled tests

Table 6.1. Data: CERAD

	Men	Women
Sample size	364	542
Number institutionalized (proportions)	181 (0.4973)	234 (0.4317)
Median Survival (years)	1	2.1
Censoring (%)	17.58	23.62

Table 6.2. Analysis: CERAD

Tests	Z_{obs}
Peto & Peto (pooled)	4.9251
Peto & Peto (combined)	5.4016
Logrank (pooled)	4.6617
Logrank (combined)	5.1630
Peto &Peto (separate)	5.2439
Logrank (separate)	4.7751
Proportions (separate)	1.9410

have a strong Z_{obs}. Peto & Peto (combined) is the strongest test ($Z_{obs} = 5.4016$), which is stronger than the Peto & Peto (separate) ($Z_{obs} = 5.2439$).

In conclusion, Peto & Peto (combined), being the most appropriate test to perform for the CERAD data, does yield the highest observed value of the Z statistic.

Demonstration of applicability of the combined test proposed in this dissertation on CERAD data is now complete.

CHAPTER 7
SUMMARY

In clinical trials when one is confronted with situations that have the same structure as our scenario, one might consider using our combined test statistic T given in equation (2.19), instead of performing separate tests or pooling nonresponders with responders. Our test statistic T requires the user to have prior knowledge of $\rho = d/c$. If ρ must be estimated then it is crucial that one estimates ρ accurately in the interest of higher power.

A pitfall in using our test T is when change in responder proportions and the change in median failure times are both close to zero. In such situations estimation of ρ may not be reliable, owing to instability in a near-(0/0) form.

Pooled tests will be identical to combined tests only when $\rho = 1$. In all other situations one can expect our combined test T to have higher power.

Our combined test is simple in structure. Moreover, T has the capability of handling both unidirectional and bidirectional hypotheses. In other words, even if the sign of the two components in T are opposite, the effects do not cancel each other out.

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BIOGRAPHICAL SKETCH

I was born Rahul Mukherjee in Calcutta, India, on 16 June 1963. Around 4-5 years of age, I had the strange notion that my name had something to do with my feeling confused in life. During a kindergarten class I pointed to the letter "R" successfully. Thrilled, I started calling myself Robin.

My family moved around the country frequently, and it was hard for me to establish a sense of belonging in any particular place. From 1972 to 1978 I attended boarding school. I completed high school in Calcutta in 1980.

My interest in scholastics did not emerge until late in my high school years, when I was fortunate enough to study with a wonderful man by the name of Mrinal Kanti Basu, my private tutor. Mr. Basu's methods were quite nonstandard. He did not teach me mathematics; actually he taught me about love, respect, learning, and perseverance. He would always say to me, "Robin, if He places a hurdle before you, and He always does, He also hides a solution that you need to find." I wish Mr. Basu were still among us today, as I owe him my subsequent academic success.

After graduating from high school with top scores in math and science I went to St. Xavier's College, Calcutta, to study economics, mathematics, and statistics at the pre-university level. I continued at St. Xavier's College to earn a B.Sc. in Mathematics in 1988.

In 1989 I joined the M.S. program at the University of Southern Mississippi, Hattiesburg, MS, earning a M.S. in Mathematics in 1991. I then enrolled in Virginia Polytechnic Institute & State University, Blacksburg, VA where I received a M.S. in statistics in 1993. Fall 1993 brought me to the University of Florida in quest of a Ph.D. in statistics. The quest has finally been fulfilled.

Starting in March 1999 I will work as a Biometrician in the CBARDS (Clinical Biostatistics and Research Data Systems) department of Merck Research Laboratories, Blue Bell, PA.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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May 1999

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